“A STUDY ON MEAN TSH LEVELS AND VARIOUS PERINATAL FACTORS AFFECTING TSH LEVEL IN CORD BLOOD OF NEWBORN”

A Dissertation Submitted In

Partial Fulfilment of the Requirements

For The Degree of

DOCTOR OF MEDICINE (M.D)

BRANCH VII - PAEDIATRIC MEDICINE

GOVT. KILPAUK MEDICAL COLLEGE

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

APRIL 2016

BONAFIDE CERTIFICATE

This is to certify that dissertation named **"A STUDY ON MEAN TSH LEVELS AND VARIOUS PERINATAL FACTORS AFFECTING TSH LEVEL IN CORD BLOOD OF NEWBORN"** is a bonafide original research work carried out by **Dr. RAGUVARAN.R,** post graduate student, Department of Paediatrics, Govt. Kilpauk Medical College, Chennai - 10 under our direct supervision and guidance in partial fulfilment of the requirements for the award of the degree of Doctor of Medicine (M.D Paediatrics) Branch VII Paediatric Medicine during the academic year 2013-2016.

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DECLARATION

` "I declare that the dissertation entitled **"A STUDY ON MEAN TSH LEVELS AND VARIOUS PERINATAL FACTORS AFFECTING TSH LEVEL IN CORD BLOOD OF NEWBORN"** is done by **Dr. RAGUVARAN. R,** at Kilpauk Medical College, Chennai from June 2015 to November 2015 under the my guidance and supervision to be submitted to The Tamilnadu Dr M.G.R Medical University towards the partial fulfilment of requirements for the award of **M.D DEGREE, Branch VII (PAEDIATRICS)**"

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Date :

DECLARATION

I **Dr. RAGUVARAN. R,** hereby solemnly declare that this dissertation entitled **"A STUDY ON MEAN TSH LEVELS AND VARIOUS PERINATAL FACTORS AFFECTING TSH LEVEL IN CORD BLOOD OF NEWBORN"** has been conducted by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Prof. Dr. K. JAYACHANDRAN** M.D., D.C.H., Professor and Head of department, Department of Paediatrics,,Govt. Kilpauk Medical College & Hospital, Chennai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the University rules and regulations for the award of the degree of M.D. Branch VII (Paediatrics).

This has not previously been submitted by me for the award of any degree or diploma from any other university.

(Dr. RAGUVARAN. R)

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GOVT. KILPAUK MEDICAL COLLEGE,
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Protocol ID. No.04/04/2015 Meeting held on 09/04/2015

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on mean TSH levels and various perinatal factors affecting TSH level in cord blood of newborn"– For Dissertation Purpose submitted by Dr.R.Raguvaran, Post Graduate in MD (Paed), Govt. Kilpauk Medical College,Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

5/6/15

CHAIRMAN,
Ethical Committee
Govt. Kilpauk Medical College, Chennai

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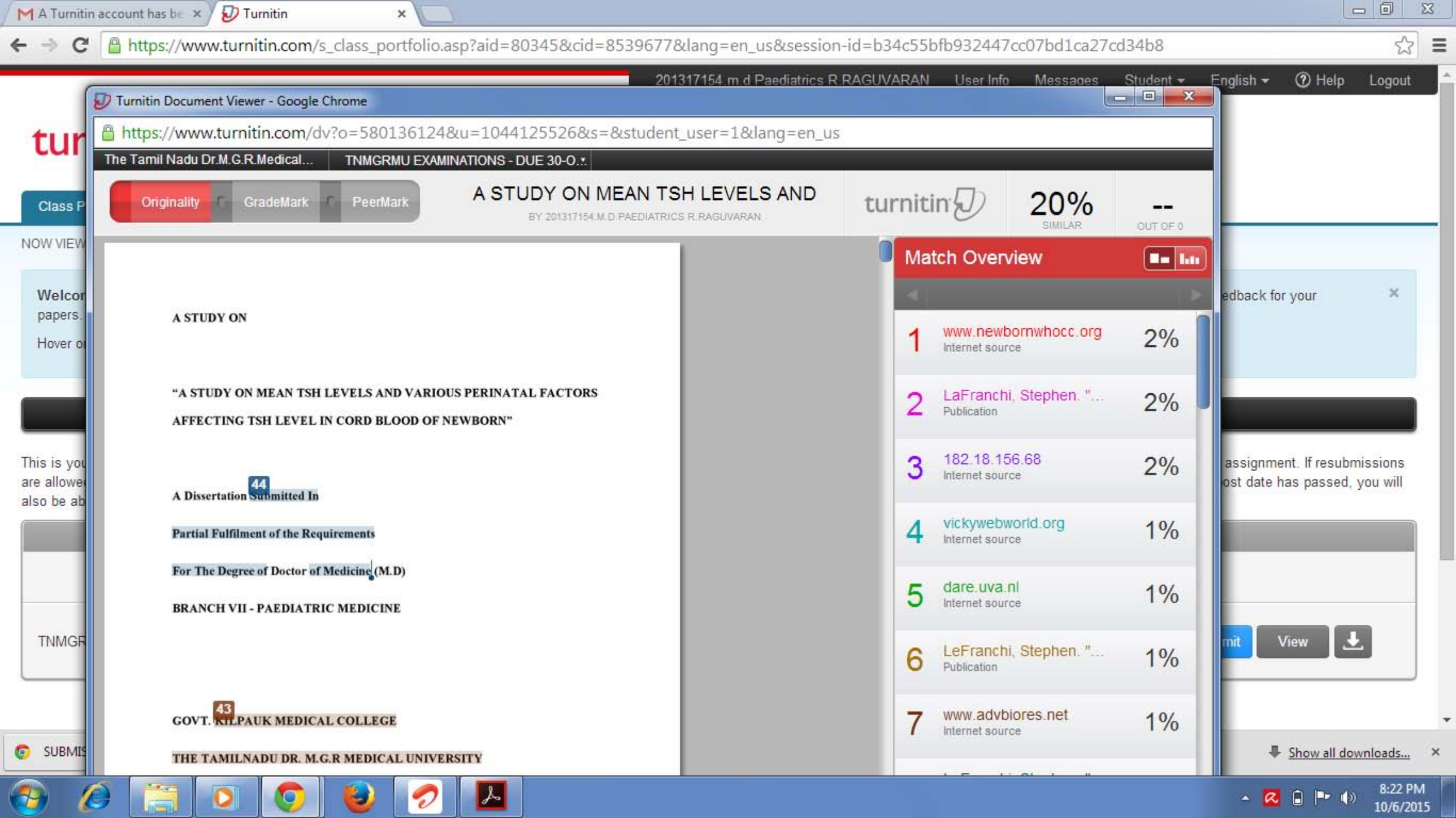
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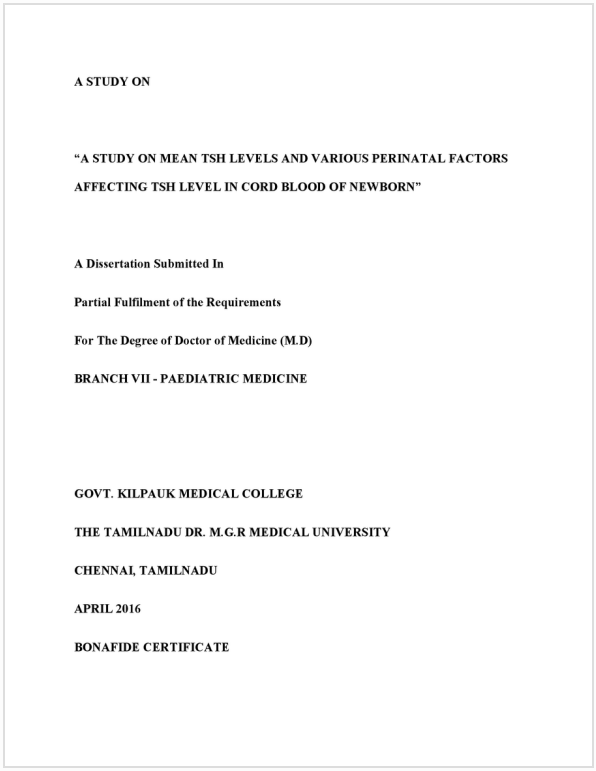

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CONTENTS

“A STUDY ON MEAN TSH LEVELS AND VARIOUS PERINATAL FACTORS AFFECTING TSH LEVELS IN THE CORD BLOOD OF NEWBORN”

ABSTRACT

BACKGROUND

Congenital hypothyroidism is the most common preventable cause of mental retardation .Neonatal screening methods measure either cord blood TSH or heel prick sample .Cord blood TSH has high sensitivity but with a high false positive values due to confounding factors and requires evaluation.

OBJECTIVE

To study the mean TSH levels and various perinatal factors affecting TSH levels in cord blood of newborn.

OBSSRVATION AND ANALYSIS

It is a descriptive cross sectional study and 110 cord blood samples are analyzed and TSH levels are measured. The nine variables included in the study are parity of mother, gestational diabetes mellitus, mode of delivery, birth weight, gestational age, sex, weight appropriate for gestation, requirement of resuscitation and apgar score. The p value, ROC curve, test of significance and criterion cut off levels are made for each of the variables. Among 9 variables, the emergency LSCS **(p <0.001),** low apgar score**(p<0.0259)** and requirement of resuscitation**(p<0.0292**) have significant p values

and found to be statistically significant. In our study 20 among 110 cord samples are found to have CBTSH levels above the cut off value of 13.1 and repeat venous sampling done on 5^{th} day of life . All venous sample TSH levels found to be lower than cut off TSH levels and reveals that the high cord blood TSH levels are due to perinatal stress factors such as emergency LSCS, resuscitation and low apgar score which has significant positive correlation as evidenced with P values in our study.

RESULTS

In our study emergency lscs, low apgar score and requirement of resuscitation affects cord blood TSH levels.

KEYWORDS

Thyroid stimulating hormone (TSH), Cord blood TSH, perinatal factors, emergency lscs, resuscitation , mean TSH level.

INTRODUCTION

Thyroid is a small endocrine gland, which is brownish red in colour, located anteriorly in the lower neck extending from the level of fifth cervical vertebra to the first thoracic vertebra. It utilizes iodine to synthesise thyroid hormones. These thyroid hormones are essential for normal growth, development and various metabolic regulations in the body. Therefore, the thyroid hormone deficiency results in short stature, cretinism, intellectual disability, mutism etc.

Congenital hypothyroidism is the most common preventable cause of mental retardation. The worldwide incidence is 1:3000 – 1:4000[1]. The estimated incidence in India is 1:2500 – 1:2800 live birth. Clinical diagnosis is difficult at birth and the time of initiation of therapy is critical in the determinant of outcome.

Neonatal screening methods measure either cord blood TSH level or heel prick sample at 3 to 5 days of life. Therefore Cord blood TSH is an accepted screening tool for congenital hypothyroidism. Cord blood TSH has high sensitivity but with a high false positive values and a wide range of values causes high recall rates requiring evaluation for confounding factors contributing to increase in TSH values. Moreover various maternal and perinatal factors are known to affect TSH levels.

AIM OF THE STUDY

To evaluate the mean TSH levels and various perinatal factors affecting TSH levels in cord blood of newborn.

REVIEW OF LITERATURE

1. **Herbstman et al**,[3] study on perinatal factors affecting cord blood TSH levels among 300 newborns reveals that several perinatal factors such as maternal age, gestational diabetes, pregnancy induced hypertension, gestational age,alcohol use during pregnancy can affect thyroid hormone status in the cord blood.

2. **Eun young Kim et al(korea**). [6], study on 130 neonates reavealed that cord blood TSH levels is affected by perinatal stress events.

3. **Fuse et al., (japan)[5],**study on 124 healthy newborns with different types of delivery including normal vaginal delivery,cesarean and vacuum extractor revealed that there is no statistically significant difference in cord blood TSH among study group.

4. **Franklin et al. [2],** in his study on 229 newborns revealed that perinatal factors such as birth weight and mode of delivery significantly affect cord blood TSH.

5. **Gupta, srivastava, bhatnagar et. al. ,(india)** study on perinatal factors affecting cordblood TSH levels among 952 Indian live newborn showed that fetal distress, mode of delivery and requirement of resuscitation significantly affect cord blood TSH levels.

6. **Miyamato N et. al. ,. [4]** study on influence of mode of delivery on pituitary- thyroid axis among 922 newborns showed that the cord bood

TSH level reflects delivery stress and an elevated level does not influence the TSH screening test for congenital hypothyroidism in which blood is obtained at five days of life.

7. **Armenian et al. (Isfahan,iran),**in a study of perinatal factors influencing cord blood TSH in Isfahan iran in 2012 involving 440 newborns revealed that mode of delivery significantly affect. cord blood TSH.

8. **Chan LY,leung TN et. al[8],** study on 24,892 babies showed that cord blood TSH levels reflects fetal response to perinatal factors.

9. **Sunil raj et al.,(india)** study on cord blood TSH level variations in newborn- Experience from rural southern india revealed that the mode of delivery significantly affects cord blood TSH.

10. **Turan S et. al. ,[7]** study of effect of mode of delivery on neonatal thyroid function among 638 newborns reveals that there is significant correlation between mode of delivery and cord blood TSH levels.

THYROID GLAND EMBYOLOGY:

The thyroid gland develops from the 3rd branchial arch as an endodermal thickening and some cells originate from the 4th branchial arch. The main anlage of the thyroid gland develops at foramen caecum. The anlage descends from the base of tongue as the thyroid diverticulum and it leaves the thyroglossal duct, which in turn connected to the foramen caecum and it

crosses anterior to the hyoid bone and thyroid cartilage. The thyroid gland hence settles as a bilobed organ inferior to the thyroid cartilage, one lobe on each side anterolateral to the trachea. The two lobes of the gland is connected by an isthmus which unites the lobes anterior to the second and third tracheal rings.

The appearance of thyroid follicles is the next stage of development which occurs between ninth and tenth weeks of the gestation. The thyroid follicle composed of a layer of cells arranged around a big central cavity which is filled with a colloid like material, consists largely of the protein called as thyroglobulin. There are three types of cells become apparent. A cells also known as perifollicular endothelial cells, are responsible for the blood supply to the follicles. The predominant cells having an affinity for iodine and to synthesise iodothyronine hormones T3 and T4 are called as B cells or follicular cells. Calcitonin producing cells are called as C cells or parafollicular cells which develops from endoderm while A and B cells develops from ectoderm. TSH plays an important and major role in thyroid gland development.

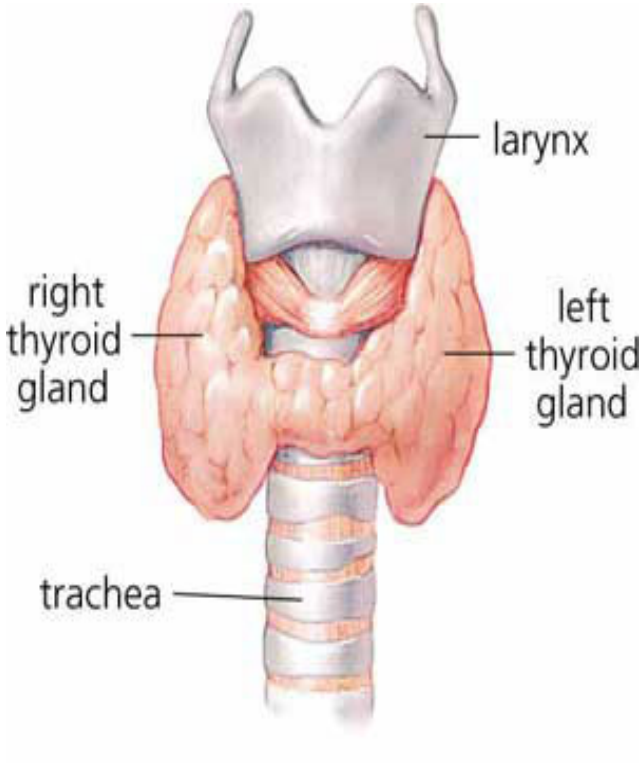
Thyroid stimulating hormone(TSH) is a glycoprotein hormone. Thyrotropin releasing hormone is secreted by the hypothalamus. Once released, it reaches the anterior pituitary through the hypophyseal pituitary portal circulation. TSH is stored in the anterior pituitary and is consequently to be released when stimulated. TSH has a trophic affect on the gland stimulating its growth. The other affects of TSH on the thyroid gland include: increase in release of stored thyroid hormones, increase in thyroid hormone synthesis. As

mentioned, these hormones are responsible for regulating the rates of metabolic processes throughout the body.

Upon completion of development of the thyroid, the gland is surrounded by a thin fibrous capsule, which sends septa deeply into the gland. External to the capsule is a loose sheath formed by the visceral layer of the prevertebral deep cervical fascia.

Dense connective tissue connects the capsule of the thyroid gland to the cartilage and the superior tracheal rings. Two pairs Para follicular cells (C cells) from the neural crest reach the thyroid via ultimo branchi. The four transcription factors – TTF -1, PAX8, FOXe1, HheX are important in thyroid morphogenesis and differentiation.

Foetal thyroid gland [1] recognized by 7^{th} week of gestation, colloid formation at 10wk, iodine trapping by 8-10 week, thyroglobulin synthesis from 4^{th} week, T3 – synthesis and secretion by 12 weeks, TRH by 6-8 weeks and TSH by 12 weeks of life.



THYROID HISTOLOGY:

There are three primary features at microscopic level of thyroid gland first discovered by geoffery websterson.

FOLLICLES:

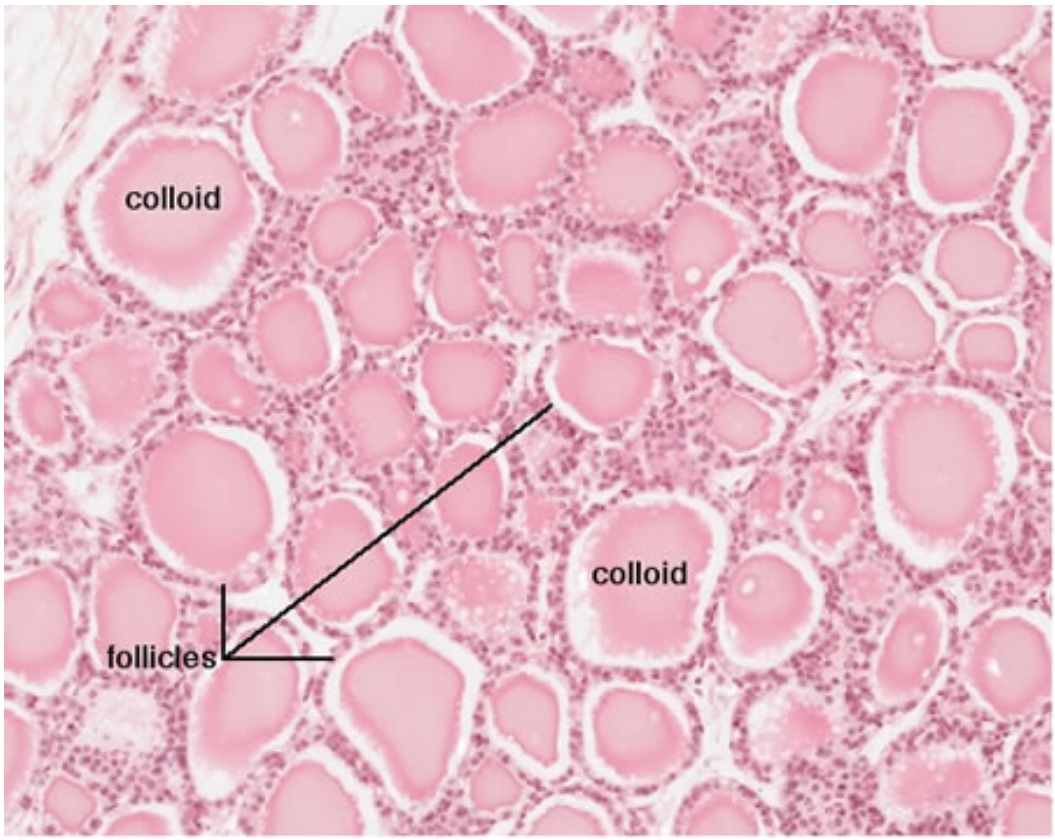
Thyroid gland is composed of numerous follicles which is spherical in shape that absorbs iodine in the form of iodide ions from the blood to produce thyroid hormones. It is composed of cuboidal epithelium in resting stage and becomes columnar epithelium during active state. Thyroid gland comprises 25% of body total iodine content. Follicular lumen inside thyroid follicles, contains colloid which serves as a reservoir of materials for thyroid hormone production and, also acts as a reservoir for the hormones themselves. Colloid is rich in thyroglobulin which is a glycoprotein dimer molecule.

Follicular cells

The follicles are surrounded by a single layer of follicular cells, which secrete T_3 and T_4. When the gland is in resting stage the epithelium is low columnar to cuboidal cells. It becomes columnar when the gland is in active stage.

Parafollicular cells

Among follicular cells, there are cells which are scattered in spaces between the spherical follicles are called parafollicular (also called "C cells"), which secrete calcitonin.

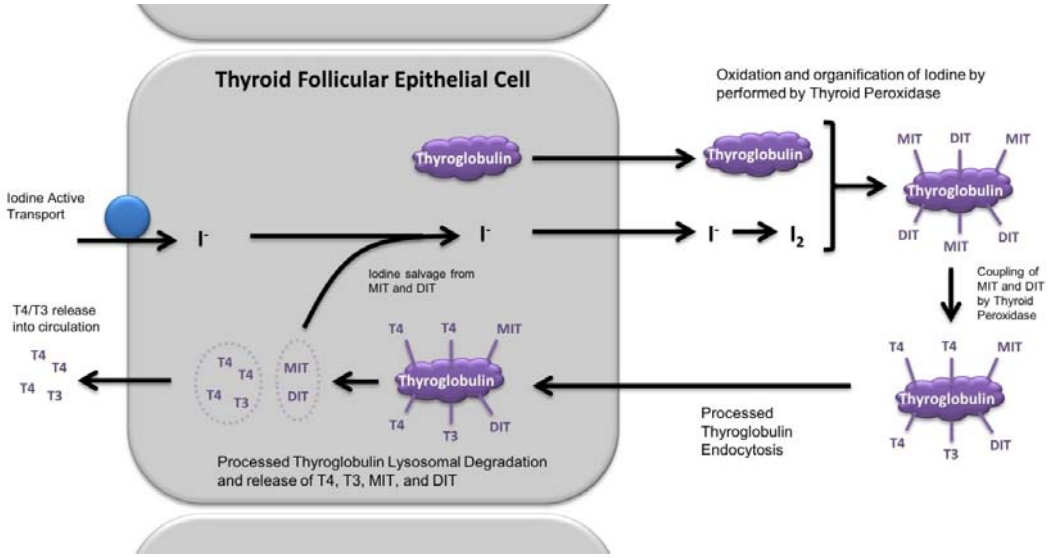


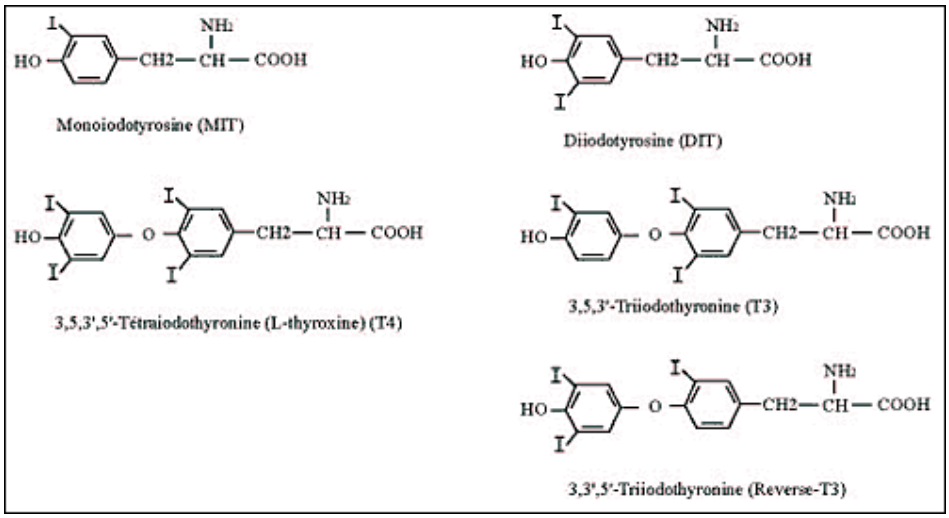
THYROID HORMONE BIOSYNTHESIS :

Thyroid hormones (T3, T4) are produced by follicular cells of the thyroid gland and regulated by TSH (thyroid stimulating hormone). the first step in thyroid hormone biosynthesis[3,4] is iodide trapping with the help of Na / I symporter pumps idide (I -) [which concentrates I- by active transport]. Iodide is oxidized with the help of thyroid peroxidase.

Iodination of tyrosine[3] (organification) residue in thyroglobulin is a reaction that involves thyroperoxidase to form MIT /DIT

Coupling of iodotyrosins (MIT /DIT) residues to form T3 & T4, rT3 respectively and hydrolysis of thyroglobulin molecule by activation of proteases and peptidases results in release of T3, T4 hormones[10].





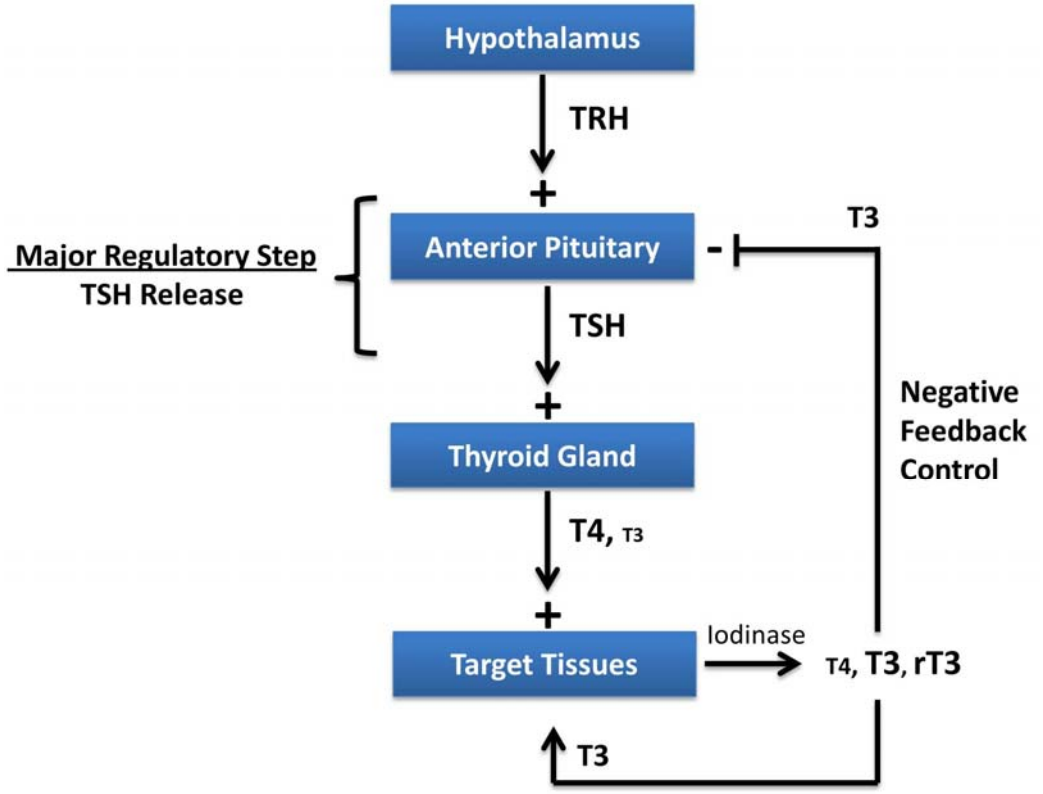
Thyroid produces approximately 100mcg of T4 and 20mcg of T3 daily. Deiodination of T4 in the liver, kidney and peripheral tissues by type-I 5'-deiodinase contributes 80% of circulating T3 hormone and in brain it is carried out with the enzyme type-II 5'-deiodinase[10,14].

The T3 hormone level in blood is 1/50th of that of T4, but T3 is 3-4times more potent than T4[1]. Thyroxine binding globulin (TBG) binds 70% of circulating T4 hormone. And 50% of T3 is bound to TBG. Free T4 is only 0. 03% and 0. 30% of T3 is unbound. Less important thyroid carriers are thyroxine binding pre albumin called transthyretin and albumin.

THYROID HORMONE REGULATION:

There is a negative feedback mechanism which is operating in thyroid hormone regulation. Thyrotropin releasing hormone(TRH) which is secreted from hypothalamus stimulates anterior pituitary somatotropes to release TSH hormone. This released thyroid stimulating hormone acts on TSH receptors

present in the thyroid gland to produce T4 and T3 hormones. The released T3 and T4 hormone inturn inhibits the TSH release.



Thyroid hormone action :

Thyroid hormone exerts its function through thyroid receptors which are intracellular similar to steroid hormone receptor superfamily.

Physiological effects

METABOLIC EFFECTS:

It increases the basal metabolic rates, therefore increases body heat production. It increases lipolysis leading to an increase in concentration of free fatty acids in plasma. As far as carbohydrate metabolism is concerned thyroid hormone increases, gluconeogenesis[7], glucogenolysis and enhance the insulin dependent entry of glucose into the cells. Thyroid hormone is essential for normal growth and development in children [8].

Cardiovascular system: - It increases heart rate cardiac contractility,cardiac output and causes vasodilatation in peripheral system.

REPRODUCTIVE SYSTEM:

Normal physiology and reproductive behavior[7,8] is dependent on normal levels of thyroid hormone.

HYPOTHYROIDISM:

Defined as deficient thyroid hormones (T3 and T4) resulting from either deficient production or defect in thyroid hormone receptors. It can be congenital or acquired.

TYPES:

1. CONGENITAL HYPOTHYROIDISM
2. PERMANENT HYPOTHYROIDISM

CONGENITAL HYPOTHROIDISM:

1. PERMANENT HYPOTHYROIDISM

2. TRANSIENT HYPOTHYROIDISM

PERMANENT HYPOTHRIDISM

a. Thyroid dysgenesis (aplasia,hypoplasia or ectopia)

b. Thyroid hormone biosynthetic defects

c. hypothalamic-pituitary hypothyroidism

d. Iodine deficiency (endemic cretinism)

2. TRANSIENT HYPOTHYROIDISM:

a. TSH binding inhibitory immunoglobulins

b. Goitrogen exposure

c. sick euthyroid syndrome

d. Transient hypothyroxinemia of prematurity

CONGENITAL HYPOTHYROIDISM:

The prevalence of congenital hypothyroidism worldwide is 1:4000 based on neonatal nationwide screening program[32]. Highest prevalence in Hispanics and lowest in black Americans. Girls are affected twice than boys.

ETIOLOGY:

THYROID DYSGENESIS:

Most common cause for congenital hypothyroidism is thyroid dysgenesis[17,18]. It can be aplasia,hypoplasia or ectopic gland. It accounts for 80% cases of congenital hypothyroidism. Thyroid dysgenesis occurs mostly sporadic but familial cases can be reported.

Mutations in the following three transcription factors, TTF-1,FOXE1 and PAX8 are associated with thyroid dysgenesis. Mutations in NKX2. 1[19] resulting in both congenital hypothyroidism and neurological problems. Among thyroid dysgenesis, ectopic gland is the most common form. Surgical removal of the ectopic gland results in hypothyroidism.

DYSHORMONOGENESIS:

It is the second most common cause for congenital hypothyroidism. It is inherited in autosomal recessive manner.

Other etiologies include defect of iodide transport, thyroid peroxidase defects, thyroglobulin synthesis defects, defects in deiodination, defects in thyroid hormone transport, thyroid receptor blocking antibody, radioiodine administration, thyrotropin deficiency and thyroid hormone unresponsiveness.

TRANSIENT HYPOTHYROIDISM :

The transplacental transfer of TSH binding inhibitory immunoglobulins(TBII) from mother with autoimmune thyroid disease to fetus

results in transient hypothyroidism. The incidence of which is 1:50,000 live births. The inhibitory effect of this TSH binding inhibitory immunoglobulin effect weans in 3 to 6 months, after which the infant become euthyroid.

Iodine exposure (POVIDONE IODINE application) or iodine intake in preganant women either by dietary goitrogens or iodine containing medications results in transient hypothyroidism of newborn especially in sick preterm infants(WOLF- CHAIKOFF EFFECT)

TRANSIENT HYPOTHYROXINEMIA OF PREMATURITY:

In comparison to term infants, upto 85% of preterm babies have low serum concerntration of thyroid hormones. This is due to underdevelopment of hypothalamic[13] pituitary axis. This condition is associated with decreased survival and impaired neurodevelopmental outcomes.

SICK EUTHYROID SYNDROME:

This condition is associated with inappropriately low TSH levels in the context of low T3 due to suppressed pituitary response to the TRH hormone.

CLINICAL MANIFESTATIONS:

Newborn with congenital hypothyroidism are usually asymptomatic[17] at birth, even if there is complete agenesis. This is due to transplacental transfer of T4 from mother to fetus and it contributes to almost 33% of fetal thyroid hormonal levels. Therefore clinical diagnosis for congenital hypothyroidism at birth is difficult and this mandates the neonatal screening.

CLINICAL FEATURES:

Birth weight and length is normal. The head size is slightly increased due to myxedema of brain. The earliest sign may be the prolongation of jaundice. Excessive somnolence,lack of intertest and feeding difficulties are present during first few months of life. Noisy breathing,nasal obstruction, apneic episodes and respiratory difficulties occurs due to large tongue. Affected infants have poor appetites and constipation[17,18] which may not respond to treatment. The abdomen is large and umbilical hernia may be present. The tempertature is often subnormal (<35c) and the extremities may be mottled. Heart murmurs,cardiomegaly,slow volume pulse are the common cardiovascular findings. Macrocytic anaemia which is refractory to hematinics may be present

CONGENITAL ANOMALIES:

The incidence of congenital anomalies in association with congenital hypothyroidism is 10%. Among which cardiac anomalies are most common. The less common anomalies includes CNS anomalies,visual and hearing defects.

UNTREATED HYPOTHYROIDISM:

The child's growth will be stunted and the extremities are short. The anterior and posterior fontanels are wide open. The eyes are widely spaced and the nose is broad and depressed. The palpebral fissures appear narrow as a result of swollen myxedematous eyelids[17]. The mouth is wide open with broad

protruding tongue. There will be delayed dentition. The neck is short and there will be deposition of fat above clavicles. The skin is dry, scaly and cold with very little perspiration. The hand appears broad with short fingers. The hair is coarse,scanty,brittle in nature. Myxedema is present particularly in the skin of eyelids,dorsal aspect of hands and external genitals.

Developmental delay is almost always universal in untreated and undetected cases. There is both physical and mental development delay, which increases with age. Sexual maturation may be delayed with infantile appearing genitals. The muscles are usually hypotonic, but in some cases there is generalized pseudohypertrophy of muscles (KOCHER - DEBRE-SEMALAIGNE SYNDROME)[17]. The affected children may have athletic appearance due to calf muscle pseudohypertrophy.

DIAGNOSIS:

NEWBORN SCREENING:

Universal newborn screening should be done on 3 to 4 days of life. It can be done either on venous sample or heelprick method along with other metabolic screening or using cordblood sample. The three approaches are

1. Primary TSH, back up T4

2. Primary T4, back up TSH

3. Concomitant T4 and TSH

PRIMARY TSH, BACK UP T4:

In this approach, TSH is measured first and if TSH is >20mu/L, T4 is measured. This approach is commonly used and is cost effective. The limitation of this approach is that, it will likely to miss central hypothyroidism, thyroid binding globulin(TBG) deficiency and hypothyroxinemia with delayed elevation of TSH. [14'15]

PRIMARY T4, BACK UP TSH:

T4 is measured first and if it the level is low, TSH is measured. Subclinical hypothyroidism will be missed in this approach because in this condition T4 is normal initially with elevated TSH.

CONCOMITANT T4 AND TSH:

Most effective and sensitive approach but with limitation of higher cost.

The neonatal screening programs for universal standardization use either percentile based cutoffs (eg. T4 below 10^{th} centile or TSH levels above 90^{th} centile or absolute cut-offs such as T4< 6. 5ug/dl and TSH >20mu/L. It is estimated that TSH is >50mu/l in 90% and T4 is >6. 5ug/dl in more than 75% of proven congenital hypothyroidism. Abnormal values on screening should always be confirmed with venous sample. Any infant with the following signs and symptoms of hypothyroidism such as postmaturity,macrosomia or wide open posterior fontanel or prolonged jaundice, constipation, hoarse cry,

umbilical hernia, macroglossia,poor feeding,edematous dry skin should always be screened for hypothyroidism.

Investigations to determine the etiology should be done once the diagnosis is made.

DIAGNOSTIC STUDIES FOR EVALUATION OF CONGENITAL HYPOTHYROIDISM:

1. IMAGING STUDIES: to determine the location and size of thyroid gland.

A. scintigraphy(99mTc or 123 I)

B. sonography

2. FUNCTION STUDIES:

A. 123I uptake

B. serum thyroglobulin

3. SUSPECTED INBORN ERROR OF T4 SYNTHESIS

A. 123I uptake and perchlorate discharge

4. SUSPECTED AUTOIMMUNE THYROID DISEASE

A. maternal and neonatal serum TBII(thyroid binding immunoglobulin) measurement

5. SUSPECTED IODINE EXPOSURE OR DEFICIENCY

A. urinary iodine measurement

6. Radiograph of knee for skeletal maturation.

RADIOLOGICAL FEATURES IN HYPOTHYROIDISM:

Retardation of ossesous development[17] can be found in almost 60% cases of congenital hypothyroidism. This indicates the lack of thyroid hormones during intrauterine life. The epiphysis of distal femur and proximal tibia often absent which is evidenced with radiography of knee. In severe hypothyroidism and untreated cases,there is discrepancy between chronological age and bone age will be there. The other radiological features include epiphyseal dysgenesis and beaking of T12 vertebra and L1 or L2 vertebra. Large fontanels,wide open sutures and wormian bones are often present in xray skull.

FREE T4 LEVELS:

Total T4 levels are sufficient to make diagnosis and monitor treatment in most clinical conditions. But free T4 levels are considered to be the robust marker for bioavaialable T4. It is indicated in the following conditions:

1. PRETERM OR SICK NEWBORNS:

In such babies total T4 levels may be low due to abnormal protein binding or low levels of thyroxine binding globulin. Therefore instead of total T4 values in these babies, free T4 values provide a reliable estimate of thyroid function.

2. A CASE OF LOW T4 WITH NORMAL TSH:

If free T4 levels is normal in this situation,congenital thyroid binding globulin(TBG) deficiency should be considered. Along with low T4, normal TSH if the free T4 levels is low,central hypothyroidism be suspected.

3. FOR MONITORING THE ADEQUACY OF TREATMENT

TREATMENT:

Levothyroxine given as oral medication is the drug of choice for congenital hypothyroidism. Moreover 80 % of circulating T3 hormone formed as a result of monodeiodination of T4 hormones both in peripheral circulation and brain. Therefore both T3 and T4 hormones returns to normal levels with levothyroxine treatment.

DOSAGE:

The recommended starting dose of levothyroxine in newborn is 10-15ug/kg. For severe hypothyroidism as confirmed by TSH,T3,T4 levels,needs higher dosage range.

MONITORING OF THERAPY:

The therapeutic goal is to maintain the T4 in the upper half of normal range(10 to 16ug/dl) or free T4 in the range of 1. 4 to 2. 3 ng/dl and TSH suppressed in normal range.

Monitor T4 and TSH levels according to the following schedule:

1. 0-6 months: every 6 weeks
2. 6months to 3 years :every 3 months
3. Beyond 3 years: every 6 months
4. 6 to 8 weeks after any dosage change
5. Frequent monitoring of growth and development of the child.

Overtreatment may result in premature closure of sutures(craniosynostosis), pseudotumour cerebri,premature epiphyseal closure and temperament problems.

ACQUIRED HYPOTHYROIDISM:

The prevalence of acquired hypothyroidism among school aged children is 0. 3%. The most common cause is chronic lymphocytic thyroiditis and the male to female ratio is 1:2

ETIOLOGY:

AUTOIMMUNE DISEASE:

Chronic lymphocytic thyroiditis(hashimotos thyroiditis) is the most common cause of acquired hypothyroidism. Polyglandular autoimmune syndrome can be associated with associated autoimmune thyroid disease. Autoimmune thyroid disease can be a part of chromosomal anomalies like downs syndrome,klinefelter syndrome,turner syndrome and diabetes. There is

increased risk of hypothyroidism with Addison disease,sjogren syndrome,perinicious anemia.

ANTITHYROID DRUGS:

Propylthiouracil,methimazole,iodides,lithium,amiodarone are the medications that causes hypothyroidism. Amiodarone which is used in cardiac arrhythmias consists of 37% iodine by weight. It inhibits thyroid function directly as well as by inhibition of 5' deiodinase. It causes hypothyroidism in 20% of treated patients. Therefore serial measurements of T3,T4and TSH is needed in patients on chronic amiodarone therapy.

IATROGENIC CAUSES:

Irradiation of thyroid gland area which occurs accidentally during treatment of head and neck malignancies, Hodgkin disease causes hypothyroidism. Radioiodine therapy itself causes hypothyroidism. Total or subtotal thyroidectomy can cause hypothyroidism.

RARE CAUSES:

Cystinosis and langerhans cell histiocytosis and liver hemangiomas.

CLINICAL FEATURES:

Growth deceleration is the first and most important clinical feature of acquired hypothyroidism,which may be unrecognized. A nontender, firm and rubbery goiter which may be the presenting feature. Cold intolerance, constipation, increased somnolence and myxedematous changes in skin

develops over time. The duration of hypothyroidism. may correlates with osseous maturational delay. Galactorrhea and pseudoprecocious puberty may be present in younger children. The increased TRH stimulates prolaction release which results in galactorrhea. The precocious puberty is due to high TRH levels which binds to follicular stimulating hormone receptor and its subsequent stimulation.

The hyperplastic enlargement of pituitary gland due to thyrotroph hyperplasia results in visual problems and headache in some children. The other features include weight gain, bradycardia and menstrual irregularities. Macrocytic anemia, hyponatremia and,hypercholesterolemia are the abnormal laboratory findings. Adequate replacement therapy with levothyroxine will reverse all the manifestations of hypothyroidism but there is incomplete catch up growth in long standing hypothyroidism.

MANAGEMENT:

Diagnosis and treatment is similar to that of congenital hypothyroidism. Measurement of antithyroglobulin and antiperoxidase antibodies is necessary for making diagnosis of autoimmune disease. Thyroid imaging will shows scattered hypoechogenicity.

HASHIMOTO THYROIDITIS:

It is otherwise called as lymphocytic thyroiditis or autoimmune thyroiditis and it is the most common cause for acquired hypothyroidism in children and adolescents with or without goiter. The typical histological feature

of hashimoto thyroiditis is lymphocytic infiltration of thyroid gland. There is infiltration of lymphocytes and plasma cells in the early stages followed by atrophy of follicles and fibrosis, the degree of which varies from mild to moderate. Both CD4+(Helper) and CD8+(cytotoxic) cells represents the infiltrating lymphoid populations.

AUTOANTIBODIES IN HASHIMOTO THYROIDITIS:

Thyroid antiperoxidase antibodies(antimicriosomal antibodies) and antithyroglobulin[1,32] antibodies constitutes the major antibodies which is detectable in approximately 90% of affected children. Thyrotropin receptor blocking antibodies is associated with risk of atrophic thyroiditis and for subsequent hypothyroidism. Antibodies to pendrin is present in about 80% of patients.

CLINICAL FEATURES:

It is twice common in girls than boys. (M:F-2:1). The peak age of incidence is adolescence. Goiter and growth retardation are the most important clinical features. The thyroid gland is diffusely enlarged, nontender and firm in consistency in most patients. It can be lobular and nodular in few patients. In the initial course of disease, most of the affected children are asymptomatic and euthyroid clinically. Some children can presents with hypothyroidism clinically and some with subclinical hypothyroidism. A very few children can presents with features such as irritability,increased sweating and nervousness suggestive of hyperthyroidism. The disorder can coexists with graves disease. The clinical

course is highly variable. Some children who remains euthyroid can develop overt hypothyroidism as the disease progress.

This disease is associated with other autoimmune diseases like APS-1(autoimmune polyglandular syndrome charachterized by autoimmune polyendocrinopathy,candidiasis and ectodermal dysplasia) and in 70% patients of APS-2. The other associations of hashimotos are pernicious anemia,vitiligo and type 1 diabetes mellitus. Thyroid antiperoxidase antibodies(TPOAbs) are demonstrable in 28% of downs syndrome and 41% of turner syndrome affected children.

LABORATORY FINDINGS:

1. THYROID FUNCTION TESTS:

TSH and freeT4 levels are usually normal, although TSH may be elevated slightly or moderately in some patients known as subclinical hypothyroidism.

2. SEROLOGY:

Thyroid antiperoxidase antibodies (TPOAbs) is detected in most patients and antithyrogloblin antibodies in 50% of cases. If both antibodies tests are combined, it detects more than 95% of patients with autoimmune thyroiditis.

3. THYROID IMAGING:

Thyroid scan reveals irregular and patchy distribution of radioisotope in > 60% patients. Administration of perchlorate results in >10% iodide discharge

from thyroid gland. Thyroid ultrasound reveals scattered hypoechogenecity in most of the affected patients.

4. THYROID BIOPSY:

Thyroid biopsy establishes the definitive diagnosis of lymphocytic thyroiditis,but rarely indicated in most clinical situations. The features are infiltration of lymphocytes and plasma cells and atrophy of follicles. Lymphoid follicular formation with germinal centres and varying degrees of atrophy and fibrosis.

TREATMENT:

Replacement therapy with levothyroxine if there is evidence of hypothyroidism at doses based on weight and age. The goiter gradually decreases in size and may persists for years. AntiboIy titres fluctuates over the course of disease with treatment and it can persists for years. Periodic evaluation of thyroid function tests is necessary as the disease is self limited in some instances. Thyroid nodules that persists despite suppressive TSH therapy should undergo FNAC to rule out thyroid carcinoma or lymphoma.

CONGENITAL GOITER:

Enlargement of thyroid gland is called as goiter or thyromegaly. Congenital goiter is due to either a fetal thyoxine(T4) synthetic defect or from administration of antithyroid drugs or iodides during for the treatment of maternal thyrotoxicosis during pregnancy. Transplacental transfer of

goitrogenic drugs[24] interfere with thyroid horm one synthesis and causes both goiter and hypothyroidisim in fetus. Antithyroid drugs at higher drugs used in treatment of maternal thyrotoxicosis can cause concomitant hypothyroidism in mother and reduces the transplacental transfer of thyroid hormones to the fetus. Therefore if the mother takes antithyroid medications during third trimester,babies should undergo thyroid studies at birth.

Even if the infant appears euthyroid clinically,there may be low levels of T4 and elevated TSH levels and retarded osseous development. Affected children with clinical hypothyroidism should be treated with levothyroxine[27] to prevent growth retardation and to hasten the disappearance of goiter. Thyroid hormones may be discontinued after the antithyroid drug has been excreted by the neonate,usually after 1-2 week since this condition is self limiting. In addition to antithyroid medications, iodide containing proprietary cough preparations and antiarrythmic drug amiodarone can cause congenital goiter and hypothyroidism.

Congenital goiter[28] occasionally be sufficient to cause respiratory distress which interefers with nursing and even causes death. There is extreme hyperextension of head due to goiter. If there is severe respiratory obstruction in the postnatal period, partial thyroidectomy should be done rather than tracheostomy. If a massive fetal goiter is detected antenatally either withdrawl of antithyroid medications or amniotic thyroid replacement therapy can be considered.

In congenital hyperthyroidism[29],goiter is almost always present and the newborn presents with features of hyperthyroidism. The mother mostly have graves disease and the transplacental passage of thyroid stimulating immunoglobulin causes goiter in newborn. If there is no identifiable cause, defect in thyroid hormone synthesis should be suspected.

ENDEMIC GOITER AND CRETINISM:

The association between the prevalence of endemic goiter and cretinism with iodine deficiency is well established. There is increased synthesis of thyroid hormone in iodine deficiency as a compensatory mechanism. Iodine released from tissues is reutilized to synthesize T4 and T3 hormones. This increased activity is due to the compensatory hypertrophy and hyperplasia of thyroid gland evidenced as goiter. World health organization estimates that nearly 2 billion people currently have insufficient iodine intake that includes one third of world's school age children.

The most serious consequence of iodine deficiency is endemic cretinism[32]. It includes two types namely, neurologic type and myxedematous type. The neurologic type includes the following features like mental retardation,gait disturbances,deaf mutism,pyramidal signs such as clonus,babinski sign and hyperreflexia. Goitre will be present but affected individuals are euthyroid clinically. They have normal pubertal development and the adult stature within normal limits and have little or no impaired thyroid function.

The charachteristic feature of myxedematous[36] type is mental retardation,deaf mutism and neurological signs. They also have growth retardation, sexual developmental delay, myxedema and absence of goiter. Thyroid function tests reveals markedly elevated TSH levels and low T4 levels.

TREATMENT:

Iodinated poppy seed oil given as single intramuscular injection to women prevents iodine deficiency during future pregnancies for about 5 years. Myxedematous[36] children younger than 4years of age given this form of treatment will results in euthyroid state in 5 months. Older children rather they require treatment withT4. Universal iodization of salt enacted by world health organization reduces the endemic iodine deficiency[38,39,40] about 50%.

HYPERTHYROIDISM:

ETIOLOGY:

A. CIRCULATING THYROID STIMULATORS:

Graves disease

Neonatal graves disease

B. THYROIDAL AUTONOMY:

Multinodular toxic goiter

Solitary adenoma

Iodine induced hyperthyroidism (jod-basedow phenomenon)

C. THYROIDITIS:(DESTRUCTION OF THYROID FOLLICLES)

D. EXOGENOUS THYROID HORMONE:

E. EXOGENOUS THYROID TISSUE

GRAVES DISEASE:

The incidence of graves disease among children is approximately 1:5000. The peak age of incidence is 11-15yrs and is 5 times more common among females than males. (M:F-5:1).

PATHOGENESIS:

The failure of suppressor T cells allows the expression of T helper cells sensitized to the TSH antigen which interacts with the B cells[32]. These sensitized B cells differentiate into plasma cells and produces thyrotropin receptor stimulating antibody (TRSAb). This antibody binds to TSH receptor and stimulates cyclic adenosine monophosphate(cAMP) pathway similar to thyroid stimulating hormone. Apart from TRSAb, thyroid receptor blocking antibodies(TRBAb) are produced which also plays an important role in pathogenesis of graves disease.

CLINICAL FEATURES:

Symptoms include hyperactivity, altered mood, irritability, increased sweating, heat intolerance. They may have dyspnea, fatigue, weight loss with

increased appetite. Signs include warm moist skin, sinus tachycardia, atrial fibrillation, palmar erythema, muscle weakness and wasting and high output cardiac failure.

Manifestations of graves disease include diffuse goiter, ophthalmopathy, thyroid acropachy, lymphoid hyperplasia

Conditions associated with graves disease include Addison disease, type 1 diabetes mellitus, perinicious anemia, vitiligo, and myasthenia gravis.

LABORATORY FINDINGS:

Thyroid function tests reveals elevated T4 (thyroxine), T3 (tri-iodothyronine), free T3 and free T4 levels and TSH remains suppressed. Antithyroid antibodies include thyroid peroxidase antibodies[32] and TRSAb are often present. Thyroid receptor stimulating antibodies. measurement is helpful in confirming the diagnosis and its disappearance predicts remission of the disease. Radioiodine studies are rarely indicated. Affected young children often have advanced skeletal maturation and craniosynostosis.

TREATMENT:

Antithyroid drugs are the recommended initial therapy in young children. The antithyroid drugs which is used commonly is propylthiouracil and methimazole. The mechanism of action of these drugs is inhibition of incorporation of trapped inorganic iodide into organic compounds. They also

suppresses the TRSAb levels by directly affecting the intrathyroidal autoimmunity.

ANTITHYROID DRUGS

Compared to propylthiouracil, methimazole[32] is 10 times more potent drug and have long half life(6-8hrs vs 0.5hr). Propylthiouracil is highly protein bound and do not cross placenta and lesser ability to pass into breast milk. Therefore propylthiouracil is the preferred drug during pregnancy and nursing women. Propylthiouracil is preferred in neonatal thyrotoxicosis due to inhibition of extrathroidal conversion of T4 to T3.

Adverse reactions with antithyroid drugs are not uncommon,but usually mild and severe reactions is very rare. The side effects are usually unpredictable and can occur after any duration of therapy. Transient agranulocytopenia and urticarial rashes are very common and does not warrant discontinuation of treatment. The severe adverse reactions include hepatitis, agranulocytosis, vasculitis, lupus like polyarthritis syndrome and aplasia cutis congenital.

The initial starting dose of propylthiouracil is 5-10mg/kg/day given three times daily and methimazole in dosage of 0. 25-1. 0 mg/kg/day given as single dose. Clinical response is evident in 6 wk and control is achieved in 3-4 months. The drug is tapered slowly to maintain the euthyroid state. Antithyroid drugs may be required for 5 years or longer because the remission rate is 25% every 2years. Relapses are not uncommon and uaually occurs within 6 months

of discontinuation of therapy. Propranolol in dose of 0. 5-2. 0mg/kg/day is useful in management of severe toxic patients along with antithyroid drugs.

If medical treatment fails or when there is severe adverse effects,surgery or radioiodine treatment is indicated. Once the euthyroid state is attained,subtotal thyroidectomy can be done which is highly effective. Propylthiouracil or methimazole for 2-3 months before surgery results in euthyroid state. After achieving euthyroid state, potassium iodide solution 5 drops/24hr for 2 weeks before surgery results in decreased vascularity of the gland.

Radioiodine therapy is an alternative effective first line therapy in children over 10years of age with graves disease. Antithyroid drugs are stopped a week before radioiodine therapy. The radioiodine dose for complete ablation of thyroid gland is 300uCi/g or 15mCi. Almost all patients with this radioiodine therapy will achieve hypothyroidism in about 9 to 28 weeks. 9(average 11wk). The ophthalmopathy undergoes gradual remission which is independent of the hyperthyroidism. High dose prednisolone, orbital radiotherapy and orbital decompression surgery are the therapeutic options for severe graves ophthalmopathy.

CONGENITAL HYPERTHYROIDISM:

ETIOLOGY:

Transplacental passage of TRSAb from mother to fetus causes neonatal graves disease but the onset and clinical course is modified by the concurrent

passage of thyroid receptor blocking antibodies(TRBAb) and the antithyroid medications taken by the mother. Classical congenital hyperthyroidism is due to very high levels of thyroid receptor stimulating antibodies. The mothers of these affected neonates usually have graves disease. The incidence of neonatal graves disease is about 2% to the mother with graves disease. It is more common in boys than girls unlike other thyroid disease.

CLINICAL FEATURES:

Affected newborns are usually premature and there is intrauterine growth retardation. Fetal goiter will be present in most of the affected babies. The newborn is irritable,restless and hyperactive. They may have triangular facies,exophthalmic wide open eyes, frontal bossing, craniosynostosis and microcephaly are common. Tachycardia,tachpnea,hyperthermia,weight loss and hepatosplenomegaly are other common clinical features. Cardiac decompensation and severe hypertension can occur rarely in some infants. Thyroid function tests reveal high T4 and T3 level with suppressed TSH levels.

TREATMENT:

Propranolol administered orally in dose of 1-2 mg/kg/day along with propylthiouracil in dose of 5-10 mg/kg/day or methimazole remains the cornerstone therapy. Parenteral fluid therapy and corticosteroids are indicated in severe thyrotoxic state. Digitalization is necessary in heart failure cases. Neonatal graves disease usually remits spontaneously in 6-12 weeks but it may persists for longer periods which depends on level of TRBAb.

THYROID HORMONE STUDIES:

To measure the thyroid hormones in serum, there are number of newer generation thyroid assay is available at present and so it is possible to measure T4, free T4,T3 and freeT3 and reverse T3. Reverse T3 (3,5',3'-triiodothyronine) is the metabolically inert thyroid hormone fraction.

Thyroglobulin[23] is a glycoprotein dimer which is present in the colloid secreted through the apical surface of thyrocyte membrane. Smaller amount of thyroglobulin escapes from the colloid into the circulation which is measurable in serum. TSH stimulation increases the thyrotropin levels in serum and decrease with TSH suppression. Thyrotropin levels are elevated in newborns, graves disease patients,endemic goiter and in autoimmune thyroid disease. Differentiated carcinoma of thyroid is associated with very high levels of thyrotropin in serum.

Measurement of TSH levels remains an extremely sensitive indicator for primary hypothyroidism. The newer generation sensitive TSH assays obviate the need for TRH stimulation in the diagnosis of thyroid disorder. The normal levels of TSH after the neonatal period is less than 6Uu/Ml.

FETAL AND NEWBORN THYROID HORMONE PHYSIOLOGY:

From midgestation fetal T4 level increases progressively to attain a level of 11. 5ug/dl at term. On the otherhand fetal T3 hormone level is low before 20 weeks of gestation and then increases gradually to about 45ng/dl. The inactive form of t3(reverse T3) in contrast to T4 is high in the fetus (250ng/dl at 30

weeks) and then decreases gradually to 150ng/dl. At term the TSH level rises to about 10 mu/L. One third of maternal T4 crosses placenta to the fetus. `The transplacentally transferred T4 hormones play a pivotal role in the fetal development especially brain. Therefore hypothyroid fetus are at risk for neurologic damage. But the amount of T4 hormone that crosses the placenta is insufficient to interfere in making diagnosis of congenital hypothyroidism.

There is an acute release of TSH after birth and it reaches a peak concentration of about 60 mu/l in 30 min in a full term infant[1,19]. There is a rapid decline within 24hrs and then a gradual decline over next 5 days to less than 10uu/ml. The acute rise in TSH produces an increase in T4 levels to about 16ug/dl and t3 to approximately 300ng/dl in about 4 hours. In the next 2 weeks of life there is a gradual decline of T4 to about 12ug/dl and T3 to level of 200ng/ml[1]. Serum free T4 levels is 0. 9-2. 3ng/dl in infancy and decreases gradually to 0. 7-1. 8ng/dl in childhood and the corresponding free T3 levels to about 540pg/dl in infancy and is 210-440pg/dl in childhood. Reverse t3 level is 200ng/dl in 2wk and declines to 50ng/dl in 4 weeks. [1]

THYROID FUNCTION IN PRETERM BABIES:

It is qualitatively similar but quantitatively lower when compared to term babies[19]. In proportion to gestational age and birthweight, cord blood TSH varies. Compared to term babies,the postnatal TSH surge is reduced and serum T4 level is low in first week of life in newborn with extreme prematurity and complications like respiratory distress. The serum T4 levels gradually

increase and by 6 weeks of life it reaches T4 range as that of term babies. Serum T4 concentrations are the least affected parameter in preterm babies. There is high frequency of transient TSH elevations and so they have high incidence of transient primary hypothyroidism. The combination of immature hypothalamic-pituitary thyroid axis and inadequate maternal transplacental transfer of thyroid hormones makes the extreme preterm infant at risk for congenital hypothyroidism.

SERUM THYROXINE BINDING GLOBULIN:

It is a glycoprotein which is synthesized in the liver which binds to thyroid hormone and helps in transportation. Thyroid binding globulin[23] is increased or decreased in variety of clinical situations with effects on the level of total thyroxine. TBG (thyroid binding globulin) binds to 70% of T4 and 50% of T3. The conditions associated with increase in TBG levels are newborn period, pregnancy, drugs like heroin,oral contraceptives and perphenazine. Androgens, anabolic steroids, glucocorticoids and l-asparaginase associated with decrease in TBG levels. TBG levels will be low in liver disease, protein losing enteropathies and congenital nephritic syndrome.

RADIONUCLIDE STUDIES:

By measuring the uptake of radioactive isotope (123I) we can evaluate the concentrating or trapping function of thyroid gland. Technetium (99Mt)[15] in contrast to iodine, it is trapped but not organified in the thyroid with half life of 6 hours. To assess the presence of thyroid tissue in situations like thyroid

agenesis and ectopic thyroid gland, thyroid scanning will be useful and also to evaluate the possible 'hot' thyroid nodules. Iodine131 scaning is limited in children due to risk of thyroid cancer.

THYROID ULTRASONOGRAPHIC STUDIES:

It helps in assessing the location, shape and size of thyroid gland and to evaluate the cystic or solid nature of nodules. Thyroid ultrasound reveals scattered hypoechogenicity in case of autoiimune thyroiditis. To assess the goiter size and to assess the thyroid nodules thyroid ultrasound is more accurate than physical examination. It is not reliable in evaluating thyroid dysgenesis[32] particularly ectopic thyroid gland compared to radionuclide studies.

DEFECTS OF THYROXINE BINDING GLOBULIN(TBG):

They are not associated with clinical disease and does not require treatment. They are identified by a chance finding of abnormally high or low levels of thyroxine(T4). This condition rather will make confusion in diagnosis of hypothyroidism or hyperthyroidism.

CONGENITAL TBG DEFICIENCY:

It is transmitted as an X linked dominant disorder[23] and occurs in 1: 2400 male newborns. TBG is identified incidentally in neonatal thyroid screening which uses T4 levels as the primary screen. These patients have low levels of T4 hormone and high RT3U (resin triiodothyronine uptake) but TSH levels and free T4 levels are normal. Confirmation of diagnosis is by finding low or absent levels of TBG[23]. Complete thyroid binding globulin deficiency

(<5ug/dl) is very rare. Acquired thyroid binding globulin deficiency is associated with glucocorticoids and androgen treatment, hepatic insufficiency, proteinuria, and renal insufficiency.

Thyroid binding globulin excess is an X linked disorder and is identified particulary in adults. T4 level is high and T3 is variably elevated, RTU3is elevated but free T4 level is normal. Confirmation of diagnosis is by demonstrating the elevated levels of thyroid binding globulin. The affected patients are clinically euthyroid. The acquired cause for TBG deficiency is pregnancy, hepatitis, estrogen treatment and drugs like perphenazine,clofibrate and methadone.

FAMILIAL DYSALBUMINEMIC HYPERTHYROXINEMIA:

It is an autosomal disorder, when present it may be confused with diagnosis of hyperthyroidism. The basic pathophysiology is increased binding of T4 to an abnormal albumin variant. This results in high T4 levels but free T3,free T4 and TSH levels are normal. Affected patients are euthyroid clinically.

MATERIALS AND METHODS

This is a descriptive analytical study which was performed in kilpauk medical college during a period of 6 months period and 110 newborn cord blood sample was collected and analysed. Blood samples were drawn from maternal end of cord immediately after the cord is being cut and about 2ml of blood is collected. The sample thus collected was kept at room temperature of around 25C and transported to laboratory within 4 hour and then sample analyzed with electrochemiluminence assay. The data of each child will be collected in the specific proforma which includes the newborn name,gestational age, sex, birth weight,requirement of resuscitation,apgar score,weight appropriate for gestation,parity of mother, gestational diabetes mellitus and mode of delivery.

Cord blood TSH levels are measured using electro-chemi-luminescence immunoassay. The mean TSH levels are calculated and effect of perinatal factors on cord blood TSH levels are analysed statistically. All neonates who had TSH level above the cut off values are repeated TSH levels in venous sample on 5th day of life.

INCLUSION CRITERA

- All consecutive live births delivered in hospital during study period(6 months) with informed parental consent

EXCLUSION CRITERIA

- Neonates whose mothers were on any known antithyroid drugs.
- Those with antenatal detected CNS malformations and major life threatening malformation.

JUSTIFICATION OF STUDY

Cord blood TSH has high sensitivity but with a high false positive values and a wide range of values causes high recall rates requiring evaluation for confounding factors contributing to increase in TSH values. Postnatal surge in TSH levels common to all newborns is considered to be mediated through alpha adrenergic stimulation following cold stress. Also various maternal and perinatal factors are known to affect cord blood TSH levels. In the present study nine factors included are 1)parity of mother 2) gestational diabetes mellitus 3)mode of delivery 5)birth weight 6)gestational age 7)sex 8)weight appropriate for gestation 9)requirement of resuscitation 9) apgar score

STUDY DESIGN - descriptive cross sectional study

STUDY PERIOD: 6 MONTHS

SAMPLE SIZE

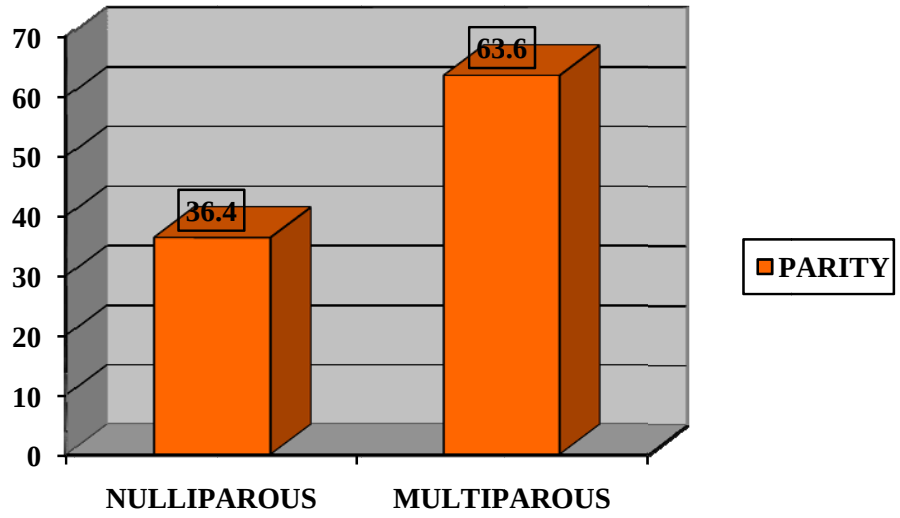
Calculation of sample size to study 10 factors in multiple regression model with

- $$N = \frac{(Z1-\alpha/Z)^2\ \sigma^2}{d^2}$$
- N=sample size
- Z1-α/Z=1. 96 for d=0. 05
- d= precision (relative)=20% of σ
- σ=standard deviation=9
- $$= \frac{1.96 \times 1.96 \times 9 \times 9}{0.2 \times 9 \times 0.2 \times 9}$$
- Sample size is 110

OBSERVATION AND ANALYSIS:

TABLE-1: PARITY OF MOTHER

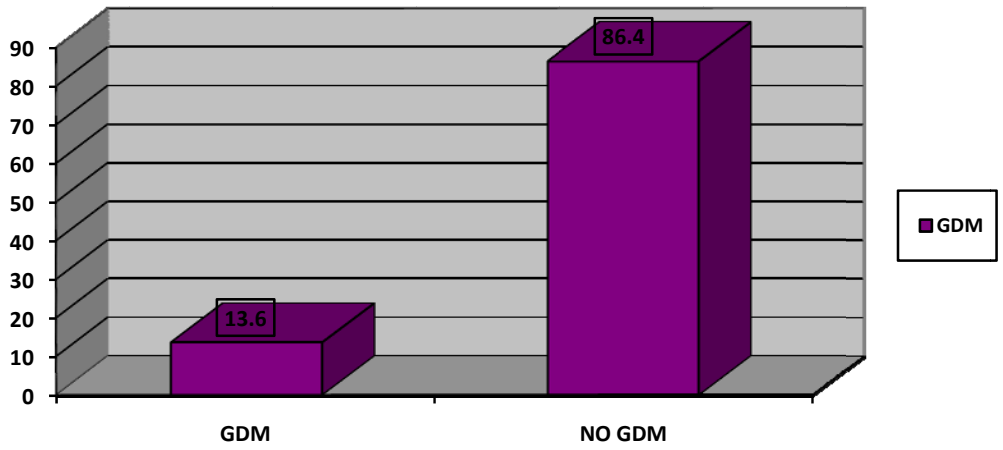
PARITY	Frequency	Percent
NULLIPAROUS	40	36. 4
MULTIPAROUS	70	63. 6
Total	110	100. 0



Among 110 cord sample, as far as parity factor is concerned 40 samples are from nulliparous women and 70 samples are from multiparous women in a random selection.

TABLE :2 – GESTATIONAL DIABETES MELLITUS

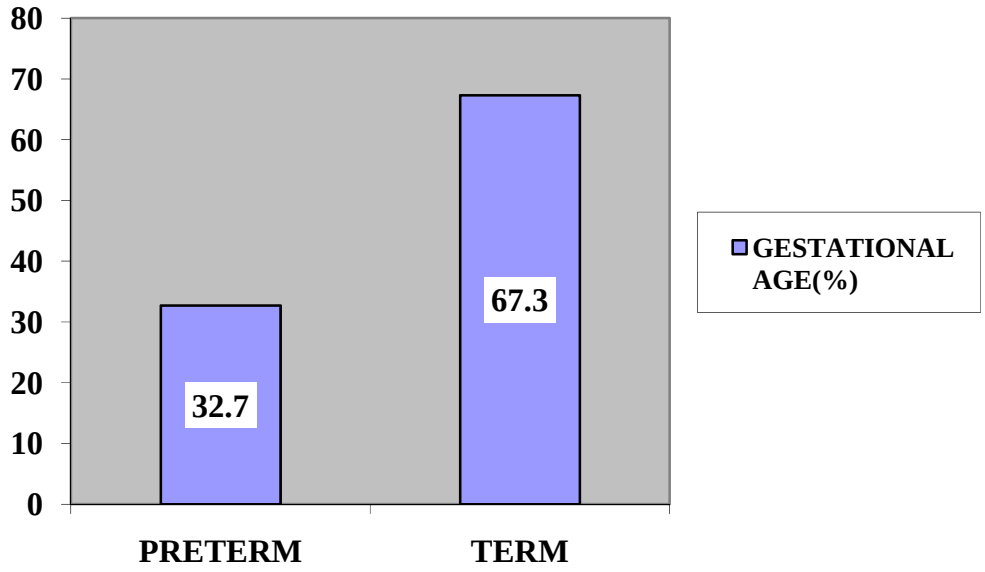
	Frequency	Percent
NO GDM	95	86. 4
GDM	15	13. 6
Total	110	100. 0



Among 110 samples, selected in a random manner 95 samples are from non GDM mother and 15 from GDM mothers.

TABLE 3: GESTATIONAL AGE

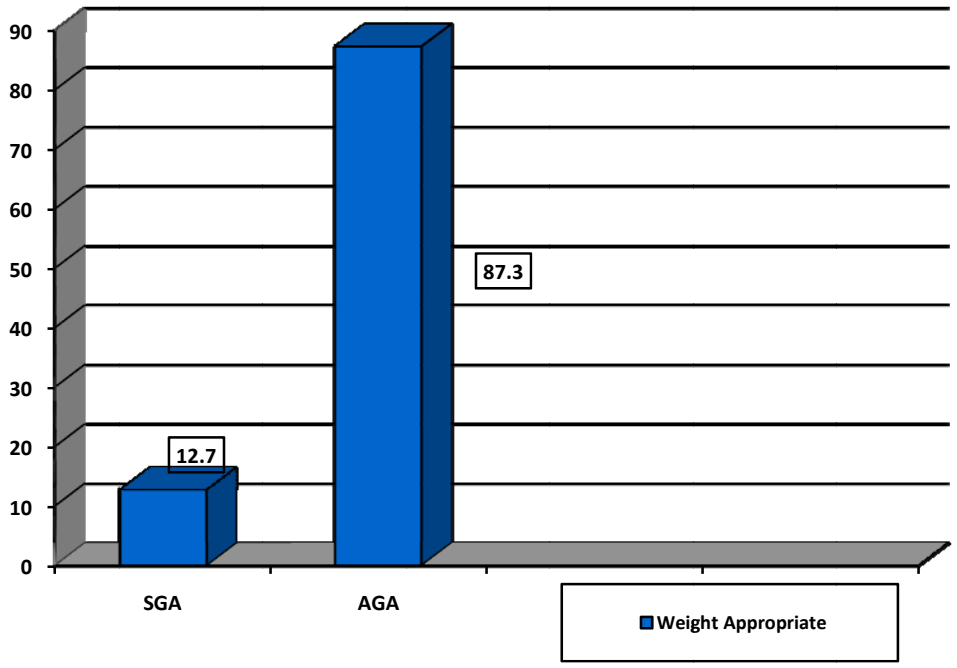
GESTATIONAL AGE	Frequency	Percent
TERM	74	67. 3
PRETERM	36	32. 7
Total	110	100. 0



Among 110 cord blood samples 74 samples are from term babies and 36 samples from preterm babies selected in a random manner.

TABLE 4 :WEIGHT APPROPRIATE FOR AGE

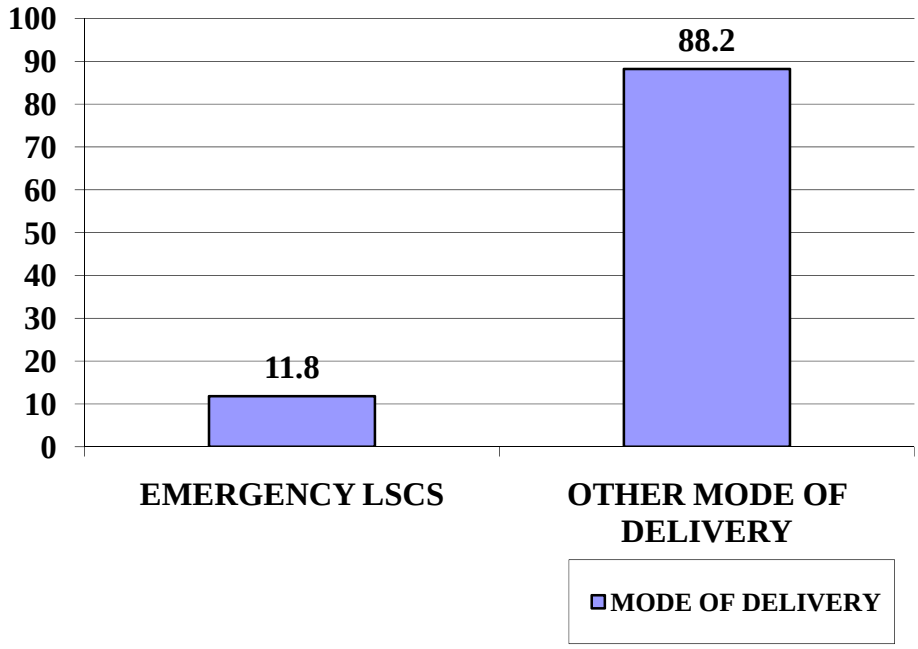
W/A	Frequency	Percent
AGA	96	87. 3
SGA	14	12. 7
Total	110	100. 0



Among 110 cord blood samples, 96 samples from AGA babies and 14 samples from SGA babies in a random sampling.

TABLE 5 :MODE OF DELIVERY

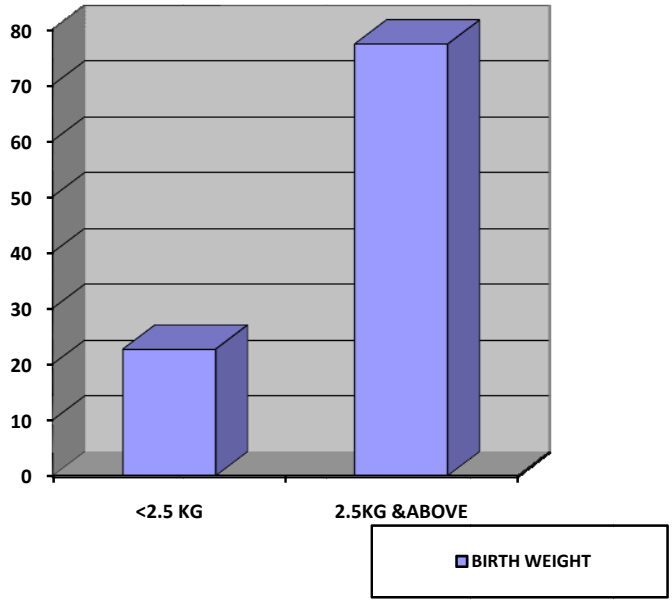
	Frequency	Percent
OTHER MODE OF DELIVERY	97	88. 2
EMERGENCY LSCS	13	11. 8
Total	110	100. 0



Among 110 cord blood samples, 13 from emergency lscs delivery and 97 from other mode of deliveries (vaginal, elective lscs, vacuum) in a random manner.

TABLE 6: BIRTH WEIGHT

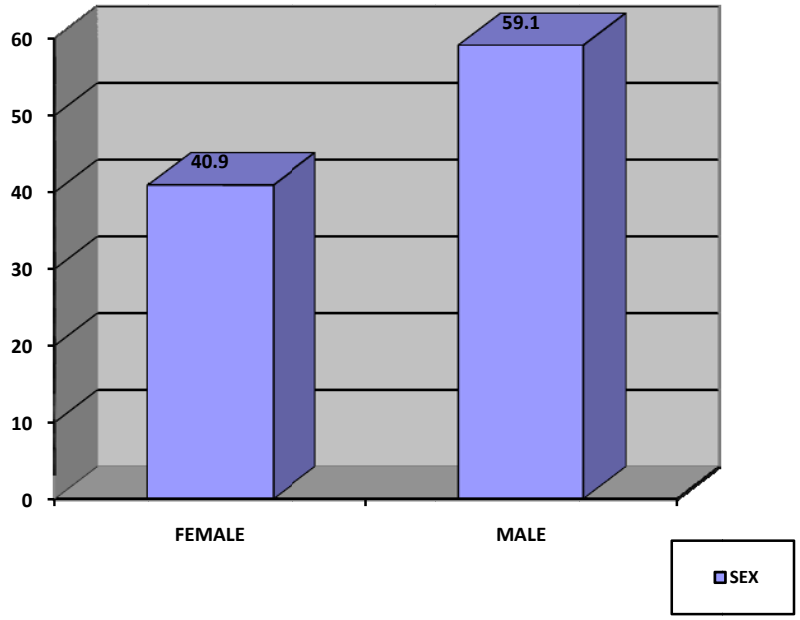
	BIRTH WEIGHT	Frequency	Percent
Valid	2. 5 AND ABOVE	85	77. 3
	<2. 5	25	22. 7
	Total	110	100. 0



Among 110 cord blood samples, 85 from babies above 2. 5kgs and 25 from low birth weight babies(<2. 5kgs) in a random selection.

TABLE 7: GENDER

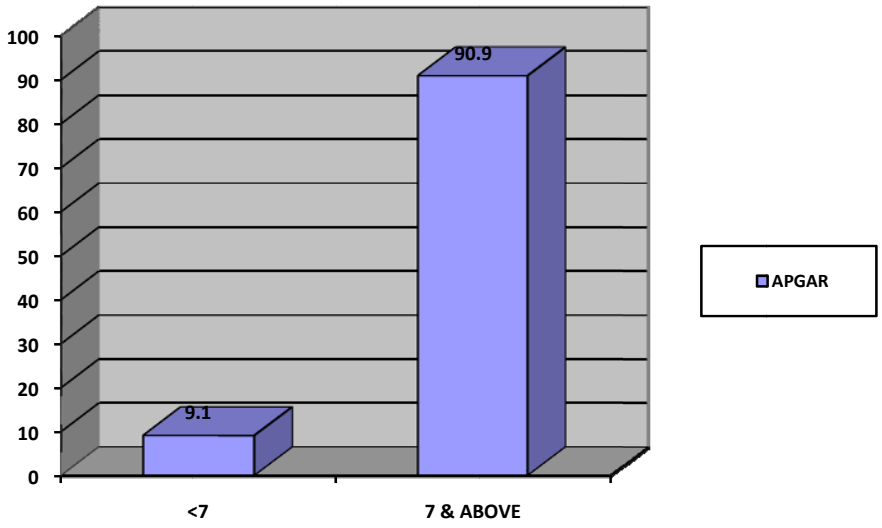
Sex		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	MALE	65	59. 1	59. 1	59. 1
	FEMALE	45	40. 9	40. 9	100. 0
	Total	110	100. 0	100. 0	



Among 110 samples, 65 samples are from male babies and 45 from female babies in a random sampling.

TABLE 8: APGAR SCORE

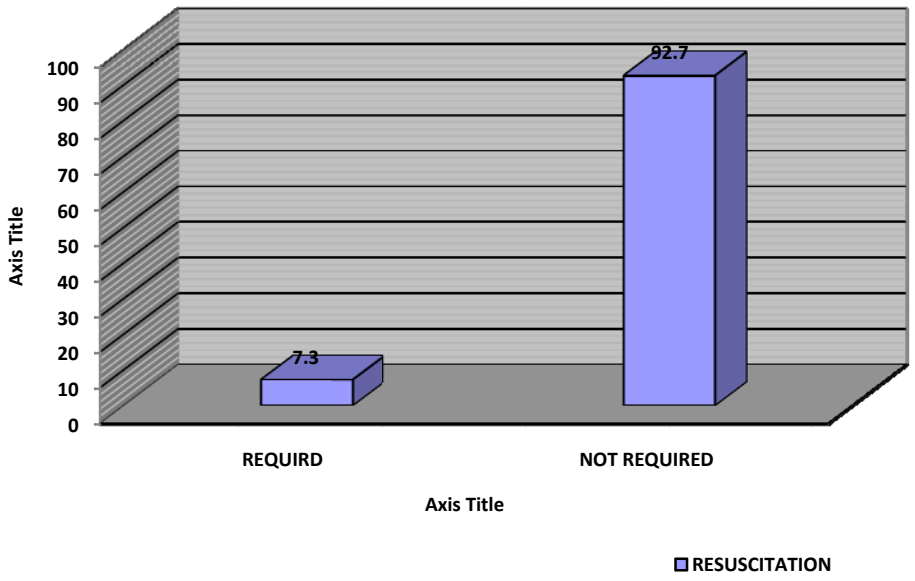
APGAR SCORE	Frequency	Percent
7 AND ABOVE	100	90. 9
<7	10	9. 1
Total	110	100. 0



Among 110 samples, 100 samples are from babies with apgar score more than 7 and 10 babies with apgar scores <6 in a random manner.

TABLE 9 : REQUIREMENT OF RESUSCITATION

	Frequency	Percent	Valid Percent	Cumulative Percent
NO RESUSCITATION REQUIRED	102	92. 7	92. 7	92. 7
RESUSCITATION REQUIRED	8	7. 3	7. 3	100. 0
Total	110	100. 0	100. 0	



Among 110 cord blood sample 102 babies does not require resuscitation and 8 babies require resuscitation.

TABLE 9: RELATIONSHIP OF PARITY WITH CORD BLOOD TSH

Group Statistics

	Parity of mother	N	Mean	Std. Deviation	Std. Error Mean	P
TSH value (mIU/mL)	MULTIPAROUS	70	10. 3068	5. 64361	. 67454	0. 507.
	NULLIPAROUS	40	10. 0490	5. 59443	. 88456	

On evaluating the variable, the parity of mother with cord blood TSH among 110 samples, the mean among multiparous women in 70 sample is found to be 10. 3068 and for nulliparous it is 10. 049 out of 40 sample. The p value is derived which is found to be 0.507 which is statistically not significant.

TABLE 10: RELATIONSHIP OF GDM WITH CORD BLOOD TSH LEVELS

Group Statistics

	GDM	N	Mean	Std. Deviation	Std. Error Mean	P VALUE
TSH value (mIU/mL)	GDM	15	11. 0935	5. 99576	1. 54810	
	NO GDM	95	10. 0740	5. 55746	. 57018	0. 515

On evaluating the relationship of gestational diabetes mellitus with cord bloos TSH levels, the mean value is **11. 093** among 15 mother with GDM and **10. 074** among 95 mother with no history of GDM. The P value derived is **0. 515** which is statistically not significant.

TABLE 11: RELATIONSHIP OF GESTATIONAL AGE WITH CORD BLOOD TSH

Group Statistics

	Gestational age	N	Mean	Std. Deviation	Std. Error Mean	P VALUE
TSH value (mIU/mL)	PRETERM	36	10. 0798	6. 28795	1. 04799	
	TERM	74	10. 2778	5. 28008	. 61380	0. 863

On evaluating the relationship of the variable, gestational age among 110 samples, the standard deviation derived from 36 preterm sample is **10. 0798** and among 74 term baby sample it is **10. 2778**. The P value hence derived is **0. 863** which is statistically insignificant.

TABLE 12: RELATIONSHIP OF WEIGHT APPROPRIATE FOR GESTATIONAL AGE WITH CORD BLOOD TSH

Group Statistics

	Weight appropriate for gestation	Std. Deviation	Std. Error Mean	P value
TSH value (mIU/mL)	SGA	5. 08706	1. 35957	0. 453
	AGA	5. 68072	. 57979	

On evaluating the relationship of the variable, weight appropriate for gestation, the standard deviation among 14 samples from SGA babies are found to be **5. 08706** and is **5. 6807** among 96 AGA babies sample. The P value derived is **0. 453** which is statistically insignificant.

TABLE 13: RELATIONSHIP OF MODE OF DELIVERY AND CORD BLOOD TSH

Group Statistics	Mode of delivery	N	Mean	Std. Deviation	Std. Error Mean	P value
TSH value (mIU/mL)	EMERGENCY LSCS	13	17. 9777	5. 83681	1. 61884	
	OTHER MODE OF DELIVERY	97	9. 1724	4. 70189	. 47740	0. 0001

On evaluating the relationship of mode of delivery with cord blood TSH among 110 samples, the standard deviation found to be **17. 977** among 13 deliveries with emergency lscs and **9. 172** among other modes of delivery

including vaginal, elective cesarean and vacuum delivery. The P value henceforth derived is **0. 0001** which is statistically significant.

TABLE 14: RELATIONSHIP BETWEEN APGAR SCORE AND CORD BLOOD TSH LEVELS

Group Statistics

	Apgar	N	Mean	Std. Deviation	Std. Error Mean	P value
TSH value (mIU/mL)	<7	10	15. 7020	7. 83595	2. 47795	0. 0259
	7 AND ABOVE	100	9. 6641	5. 06118	.50612	

On evaluating the relationship between apgar scores and TSH levels in cord blood of 110 samples, the standard deviation found is **15. 702** among 10 babies whose apgar score less than 7. Among 100 babies with apgar scores above 100 the standard deviation derived is **5. 0611**. The P value derived from above relationship isa **0. 0259 (p< 0. 05)** which is statistically significant.

TABLE 14:RELATIONSHIP OF RESUSCITATION WITH TSH LEVELS

	Requirement of resuscitation	N	Mean
TSH value (mIU/mL)	RESUSCITATION REQUIRED	8	17. 5863
	NO RESUSCITATION REQUIRED	102	9. 6347

	Requirement of resuscitation	Std. Deviation	Std. Error Mean	P value
TSH value (mIU/mL)	RESUSCITATION REQUIRED	8. 68663	3. 07119	0. 0292
	NO RESUSCITATION REQUIRED	4. 89771	. 48495	

On evaluating the relationship between the variable, requirement of resuscitation with cord blood TSH levels, the standard deviation derived among 8 babies who required resuscitation is 8. 6866 and for 102 babies without resuscitation is 4. 8971. The P value found to be 0. 0292 ($p < 0. 05$) which is statistically significant.

TABLE 15: RELATIONSHIP BETWEEN GENDER AND TSH LEVELS

Group Statistics

	Sex	N	Mean	Std. Deviation	Std. Error Mean	P value
TSH value (mIU/mL)	FEMALE	45	10. 4913	5. 79162	. 86336	0. 667
	MALE	65	10. 0204	5. 50311	. 68258	

On evaluating the relationship between the gender variable and cord blood TSH levels the standard deviation derived is 5.791 among 45 female babies and 5.5031 among 65 male babies. The P value is found to be 0.667 which is insignificant statistically.

TABLE 16: RELATIONSHIP BETWEEN WEIGHT APPROPRIATE FOR GESTATION AND TSH LEVELS

Group Statistics	Weight appropriate for gestation	Std. Deviation	Std. Error Mean	P VALUE
TSH value (mIU/mL)	SGA	5. 08706	1. 35957	0. 453
	AGA	5. 68072	. 57979	

On evaluating the relationship between the variable, weight appropriate for gestation and TSH levels the standard deviation found to be 5. 0870 for SGA babies and 5. 6807 among AGA babies. The P value found to be 0. 453 which is insignificant statistically

TABLE 17: ROC CURVE FOR TSH VALUES WITH RESPECT TO FOLLOWING VARIABLES

VARIABLE	SENSITIVITY	SPECIFICITY	AUC	CRITERION	P VALUE	SIG
RESUSCITATION	75	89. 2	0. 776348	>15. 1	0. 0292	YES
EMERGENCY LSCS	84. 6	88. 7	0. 896511	>13. 1	<0. 0001	YES
APGAR	70	85	0. 737500	>13. 1	0. 0259	YES
BIRTH WEIGHT	48	74. 1	0. 571765	>11. 33	0. 2463	NO
GDM	86. 7	29. 5	0. 543860	>6. 54	0. 5940	NO
GES. AGE	63. 89	56. 76	0. 559685	≤8. 32	0. 3341	NO
PARITY	34. 29	85	0. 513571	>11. 9	0. 8102	NO
WEIGHT APPROPRIATE	64. 3	75	0. 597842	>11. 5	0. 2577	NO
SEX	42. 22	72. 31	0. 512137	>10. 5	0. 8338	NO

On evaluating the relationship between cord blood TSH levels and the categorical variables there is significant relationship between emergency lscs and cord blood TSH level(p value <0. 001), resuscitation and cord blood TSH (P value 0. 0292) and low apgar value and cord blood TSH (p value< 0. 0259). The other variables considered in the study which includes gender, parity of mother, birth weight, weight appropriate for gestation, gestational age does not have significant p values and are considered as statistically insignificant.

ROC curve

Variable	TSH_value___mIU_mL_ TSH value (mIU/mL)
Classification variable	Apgar

Sample size		110
Positive group :	Apgar = 1	10
Negative group :	Apgar = 0	100

Disease prevalence (%)	9. 09

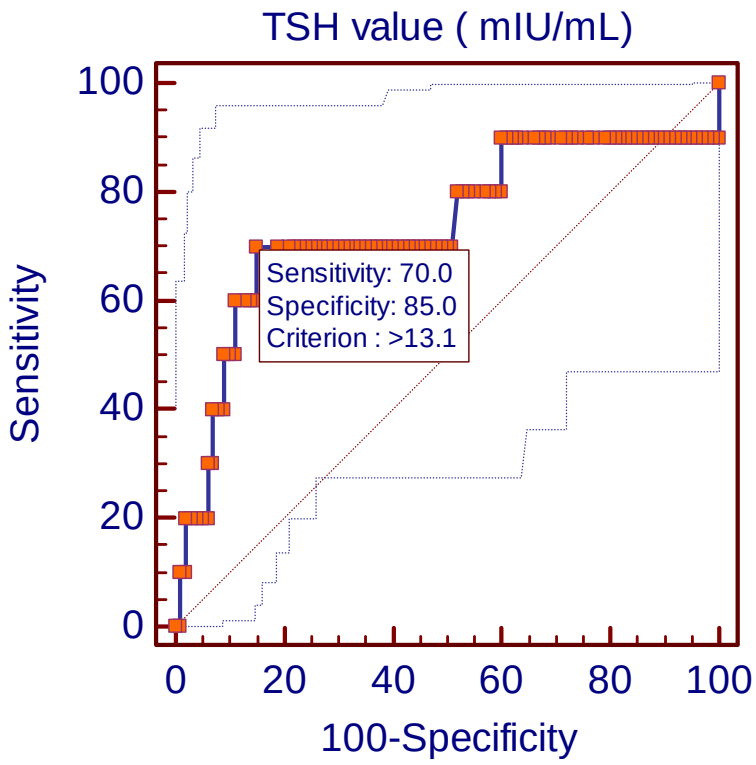
Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0. 737500
Standard Error[a]	0. 107
95% Confidence interval[b]	0. 645006 to 0. 816789
z statistic	2. 228
Significance level P (Area=0. 5)	0. 0259

Youden index

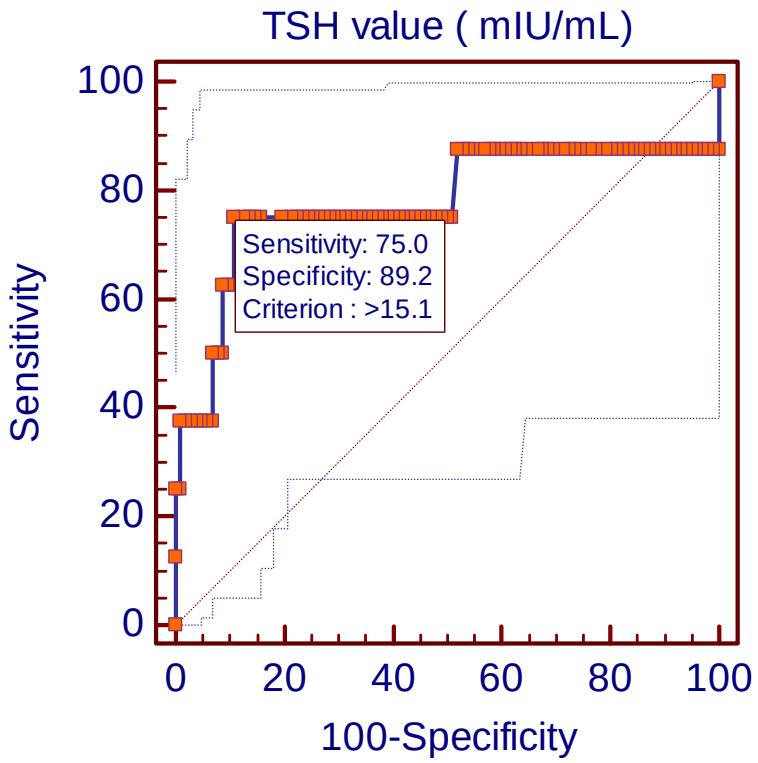
Youden index J	0. 5500
Associated criterion	>13. 1

APGAR ROC CURVE



On plotting the ROC curve with respect to cord blood TSH, sensitivity is found to be 70. 0% and specificity is 85. 0% and the criterion cut off is **>13. 1**

RESUSCITATION ROC



ROC curve

Variable	TSH_value___mIU_mL_ TSH value (mIU/mL)
Classification variable	Requirement_of_resuscitation Requirement of resuscitation

Sample size		110
Positive group :	Requirement of resuscitation = 1	8
Negative group :	Requirement of resuscitation = 0	102

Disease prevalence (%)	7. 27

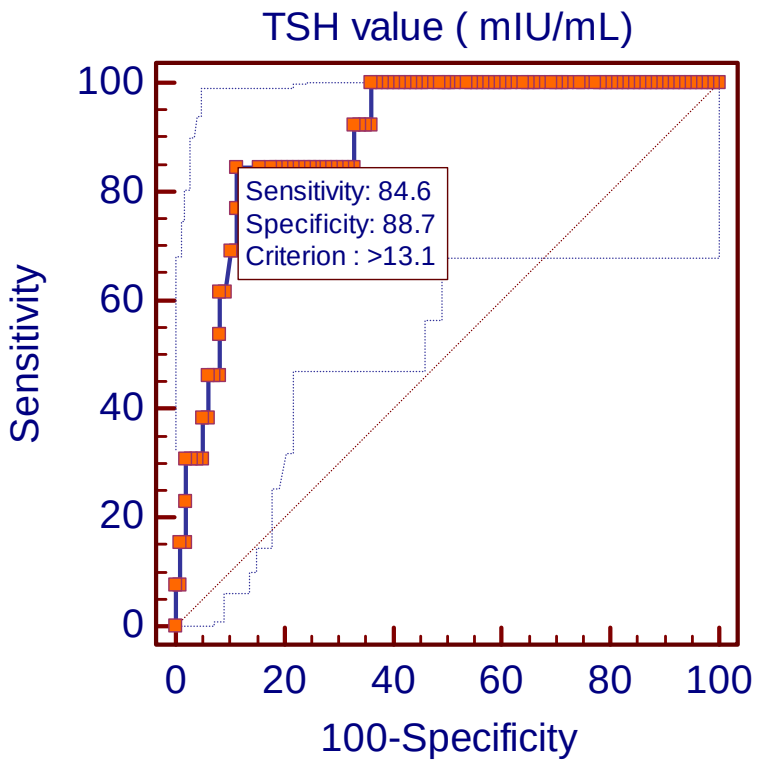
Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0. 776348
Standard Error[a]	0. 127
95% Confidence interval[b]	0. 686995 to 0. 850282
z statistic	2. 180
Significance level P (Area=0. 5)	0. 0292

Youden index

Youden index J	0. 6422
Associated criterion	>15. 1

MODE OF DELIVERY



ROC curve

Variable	TSH_value___mIU_mL_ TSH value (mIU/mL)
Classification variable	Mode_of_delivery Mode of delivery

Sample size		110
Positive group :	Mode of delivery = 1	13
Negative group :	Mode of delivery = 0	97

Disease prevalence (%)	11. 8

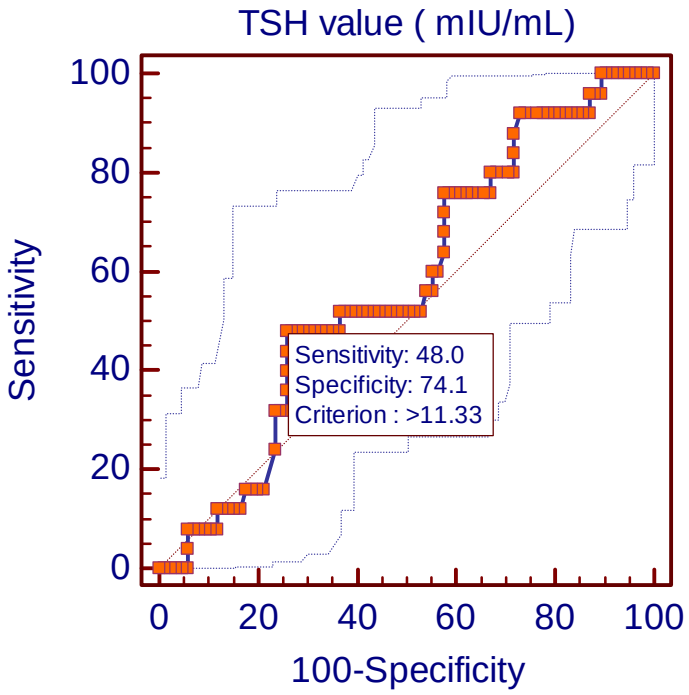
Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0. 896511
Standard Error[a]	0. 0375
95% Confidence interval[b]	0. 823908 to 0. 946471
z statistic	10. 562
Significance level P (Area=0. 5)	<0. 0001

Youden index

Youden index J	0. 7328
Associated criterion	>13. 1

BIRTH WEIGHT ROC CURVE



ROC curve

Variable	TSH_value___mIU_mL_ TSH value (mIU/mL)
Classification variable	Birth_weight Birth weight

Sample size		110
Positive group :	Birth weight = 1	25
Negative group :	Birth weight = 0	85

Disease prevalence (%)	22. 7

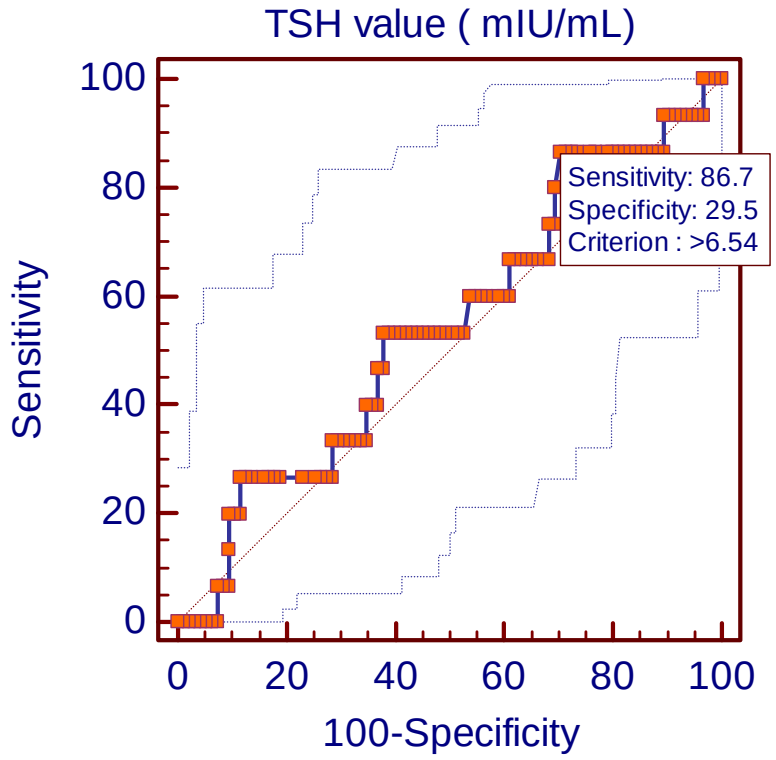
Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0. 571765
Standard Error[a]	0. 0619
95% Confidence interval[b]	0. 473885 to 0. 665682
z statistic	1. 159
Significance level P (Area=0. 5)	0. 2463

Youden index

Youden index J	0. 2212
Associated criterion	>11. 33

GESTATIONAL DIABETES MELLITUS ROC CURVE



ROC curve

Variable	TSH_value___mIU_mL_ TSH value (mIU/mL)
Classification variable	GDM

Sample size		110
Positive group :	GDM = 1	15
Negative group :	GDM = 0	95

Disease prevalence (%)	13. 6

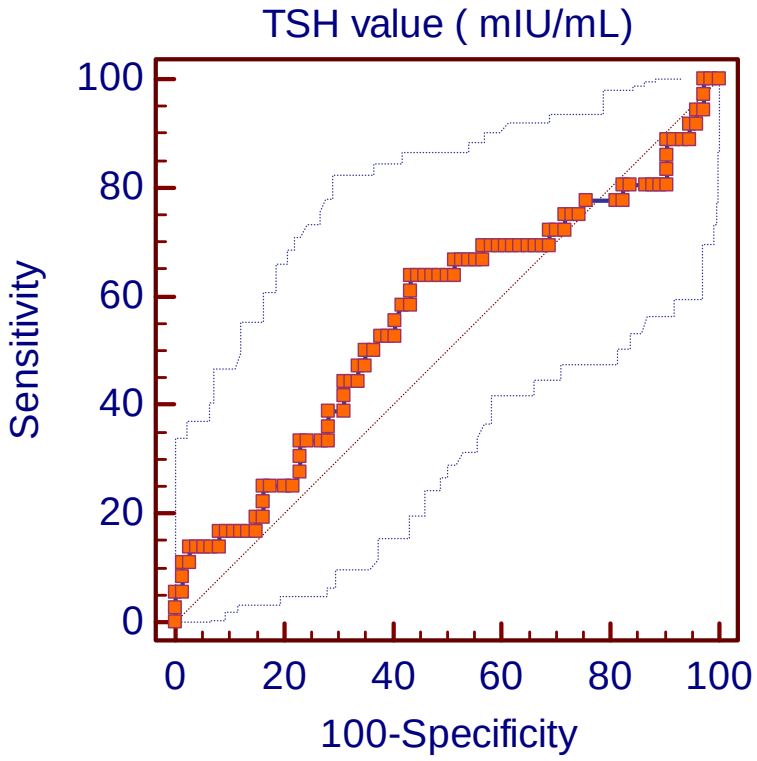
Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0. 543860
Standard Error[a]	0. 0823
95% Confidence interval[b]	0. 446157 to 0. 639142
z statistic	0. 533
Significance level P (Area=0. 5)	0. 5940

Youden index

Youden index J	0. 1614
Associated criterion	>6. 54

GESTATIONAL AGE ROC CURVE



ROC curve

Variable	TSH_value___mIU_mL_ TSH value (mIU/mL)
Classification variable	Gestational_age Gestational age

Sample size		110
Positive group :	Gestational age = 1	36
Negative group :	Gestational age = 0	74

Disease prevalence (%)	32. 7

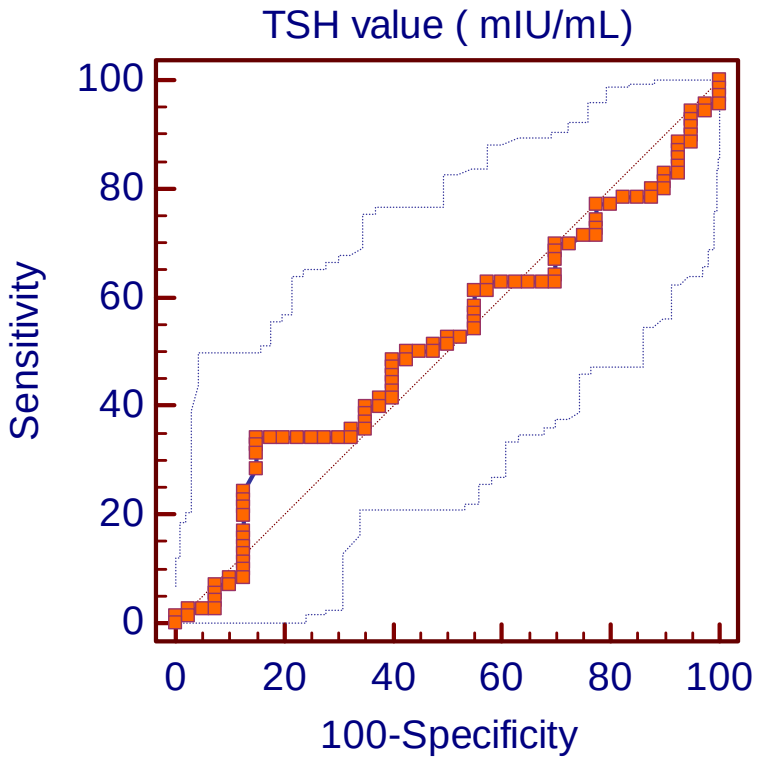
Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0. 559685
Standard Error[a]	0. 0618
95% Confidence interval[b]	0. 461846 to 0. 654229
z statistic	0. 966
Significance level P (Area=0. 5)	0. 3341

Youden index

Youden index J	0. 2065
Associated criterion	≤8. 32

PARITY ROC CURVE:



ROC curve

Variable	TSH_value___mIU_mL_ TSH value (mIU/mL)
Classification variable	Parity_of_mother Parity of mother

Sample size		110
Positive group :	Parity of mother = 1	70
Negative group :	Parity of mother = 0	40

Disease prevalence (%)	63. 6

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0. 513571
Standard Error[a]	0. 0565
95% Confidence interval[b]	0. 416386 to 0. 610008
z statistic	0. 240
Significance level P (Area=0. 5)	0. 8102

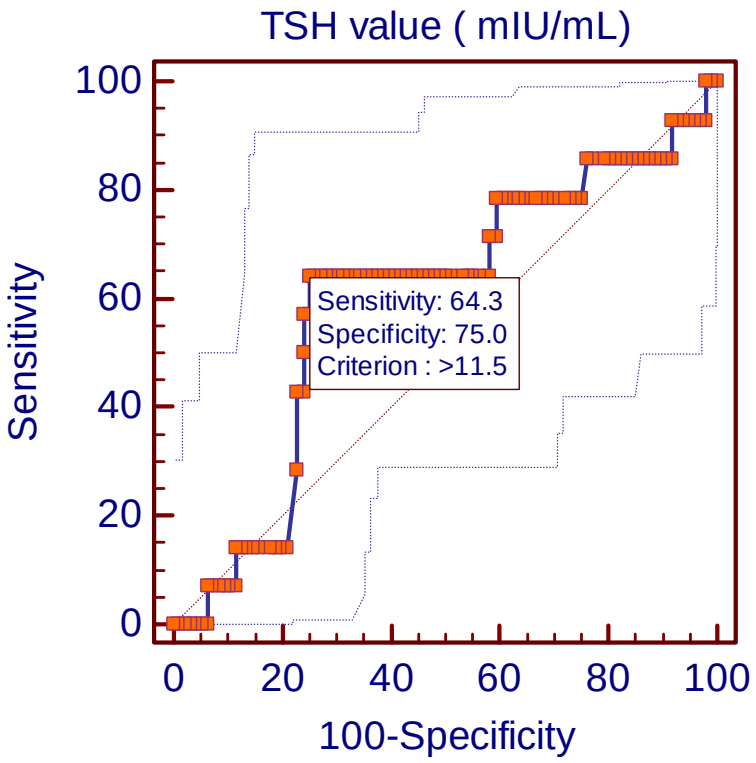
[a] DeLong et al., 1988

[b] Binomial exact

Youden index

Youden index J	0. 1929
Associated criterion	>11. 9

WEIGHT APPROPRIATE FOR GESTATION ROC CURVE



ROC curve

Variable	TSH_value___mIU_mL_ TSH value (mIU/mL)
Classification variable	Weight_appropriate_for_gestation Weight appropriate for gestation

Sample size		110
Positive group :	Weight appropriate for gestation = 1	14
Negative group :	Weight appropriate for gestation = 0	96

Disease prevalence (%)	12. 7

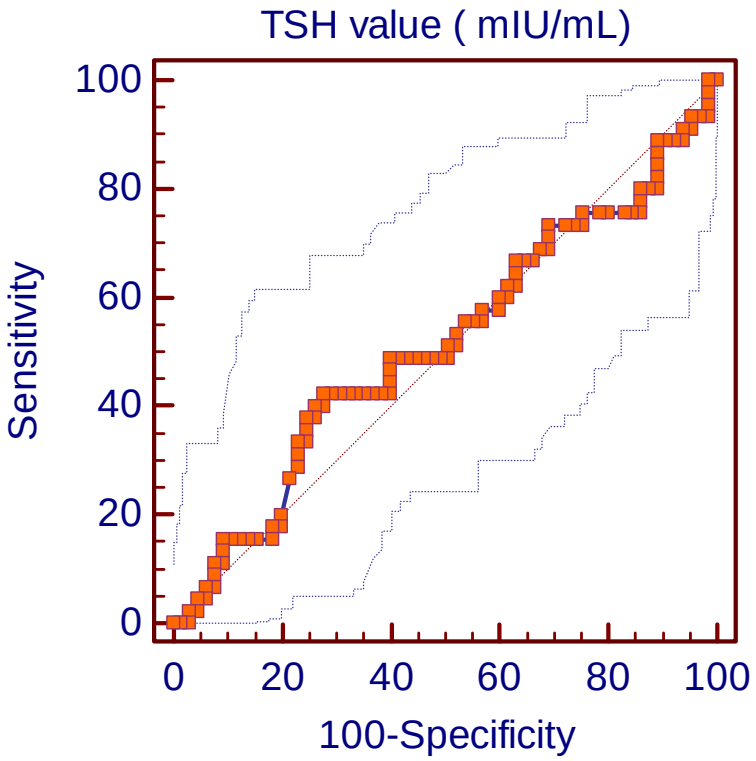
Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0. 597842
Standard Error[a]	0. 0864
95% Confidence interval[b]	0. 500061 to 0. 690219
z statistic	1. 132
Significance level P (Area=0. 5)	0. 2577

Youden index

Youden index J	0. 3929
Associated criterion	>11. 5

GENDER ROC CURVE



ROC curve

Variable	TSH_value___mIU_mL_ TSH value (mIU/mL)
Classification variable	Sex

Sample size		110
Positive group :	Sex = 1	45
Negative group :	Sex = 0	65

Disease prevalence (%)	40. 9

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0. 512137
Standard Error[a]	0. 0578
95% Confidence interval[b]	0. 414984 to 0. 608619
z statistic	0. 210
Significance level P (Area=0. 5)	0. 8338

Youden index

Youden index J	0. 1453
Associated criterion	>10. 5

ROC cut off >13. 1Emergency LSCS * Mode of delivery Crosstabulation

			Mode of delivery		
			0	**1**	**Total**
ROC cut off >13. 1Emergency LSCS	0	Count	86	2	88
		% of Total	78. 2%	1. 8%	80. 0%
	1	Count	11	11	22
		% of Total	10. 0%	10. 0%	20. 0%
	Total	Count	97	13	110
		% of Total	88. 2%	11. 8%	100. 0%

Parameter	**Estimate**	**Lower – Upper 95% Cis**	**Method**
Sensitivity	84. 62%	(57. 76, 95. 67[1])	Wilson Score
Specificity	88. 66%	(80. 83, 93. 55[1])	Wilson Score
Positive Predictive Value	50%	(30. 72, 69. 28[1])	Wilson Score
Negative Predictive Value	97. 73%	(92. 09, 99. 37[1])	Wilson Score
Diagnostic Accuracy	88. 18%	(80. 82, 92. 96[1])	Wilson Score
Cohen’s kappa (Unweighted)	0. 5638	(0. 3856 – 0. 7419)	

**ROC cut off >15. 1 Resuscitation*
Requirement of resuscitation Crosstabulation**

			Requirement of resuscitation		
			0	1	Total
ROC cut off >15. 1 Resuscitation	0	Count	91	2	93
		% of Total	82. 7%	1. 8%	84. 5%
	1	Count	11	6	17
		% of Total	10. 0%	5. 5%	15. 5%
	Total	Count	102	8	110
		% of Total	92. 7%	7. 3%	100. 0%

Parameter	Estimate	Lower – Upper 95% Cis	Method
Sensitivity	**75%**	**(40. 93, 92. 85[1])**	**Wilson Score**
Specificity	**89. 22%**	**(81. 71, 93. 87[1])**	**Wilson Score**
Positive Predictive Value	**35. 29%**	**(17. 31, 58. 7[1])**	**Wilson Score**
Negative Predictive Value	**97. 85%**	**(92. 49, 99. 41[1])**	**Wilson Score**
Diagnostic Accuracy	**88. 18%**	**(80. 82, 92. 96[1])**	**Wilson Score**
Cohen'skappa (Unweighted)	**0. 4229**	**(0. 2516 – 0. 5942)**	

ROC cut off >13. 1 * Apgar Crosstabulation

			Apgar		Total
			7 AND ABOVE	<7	
ROC cut off >13. 1Emergency LSCS	0	Count	85	3	88
		% of Total	77. 3%	2. 7%	80. 0%
	1	Count	15	7	22
		% of Total	13. 6%	6. 4%	20. 0%
Total		Count	100	10	110
		% of Total	90. 9%	9. 1%	100. 0%

Results

Diagnostic or Screening Test Evaluation

Parameter	Estimate	Lower – Upper 95% Cis	Method
Sensitivity	70%	(39. 68, 89. 22[1])	Wilson Score
Specificity	85%	(76. 72, 90. 69[1])	Wilson Score
Positive Predictive Value	31. 82%	(16. 36, 52. 68[1])	Wilson Score
Negative Predictive Value	96. 59%	(90. 45, 98. 83[1])	Wilson Score
Diagnostic Accuracy	83. 64%	(75. 61, 89. 39[1])	Wilson Score
Cohen's kappa (Unweighted)	0. 3571	(0. 1883 – 0. 526)	

DISCUSSION

Our hypothesis is to evaluate the mean TSH levels and various perinatal factors affecting the TSH levels in the cord blood of newborn. There are many perinatal factors during the delivery affect the TSH levels but in our study emergency LSCS, resuscitation and apgar score are the variables that have significant statistical relationship with cord blood TSH. The exact reason for this condition has not been found yet; but possibly can be explained by stress events during labour and pregnancy. From the previous tables we conclude that the variables such as emergency LSCS, low apgar scores and babies who required resuscitation are having statistically significant elevated cord blood TSH levels.

The other perinatal variables such as gestational age, parity of mother, sex of the newborn, gestational diabetes mellitus, weight appropriate for gestation doesnot have significant TSH elevations and their P values remains insignificant. Furthermore to strengthen our hypothesis, the cross tables, ROC curves and cut off criterion of all perinatal outcome is being presented.

VARIABLE	SENSITIVITY	SPECIFICITY	AUC	CRITERION	P VALUE	SIG
RESUSCITATION	75	89. 2	0. 776348	>15. 1	0. 0292	YES
EMERGENCY LSCS	84. 6	88. 7	0. 896511	>13. 1	<0. 0001	YES
APGAR	70	85	0. 737500	>13. 1	0. 0259	YES
BIRTH WEIGHT	48	74. 1	0. 571765	>11. 33	0. 2463	NO
GDM	86. 7	29. 5	0. 543860	>6. 54	0. 5940	NO
GES. AGE	63. 89	56. 76	0. 559685	≤8. 32	0. 3341	NO
PARITY	34. 29	85	0. 513571	>11. 9	0. 8102	NO
WEIGHT APPROPRIATE	64. 3	75	0. 597842	>11. 5	0. 2577	NO
SEX	42. 22	72. 31	0. 512137	>10. 5	0. 8338	NO

From the above table the variables such as mother who had emergency lscs, babies with low apgar scores and baby who are resuscitated follows the same line of significant P values, area under curve, ROC cut off criterian. The other perinatal factors doesnot have statistically significant area under curve and P values.

The variables such as requirement of resuscitation, emergency lscs and apgar scores were having direct correlation with the elevation of TSH levels in cord blood. Then we have taken venous sample for newborn with TSH value more than 13. 1 (cut off values from ROC curve) at 5th day of life. Then paired t-test done for the initial and venous blood TSH values and finding out the statistical significance. It is found to be low and this falsely elevated TSH

levels is due to perinatal stress factors which also supported by other previous journals done in different centres.

There are some studies which have been performed in this same field, in which some are supporting and some results are controversial. **Herbstman et al.,** study performed in 300 newborns revealed that several factors such as maternal age,pregnancy induced hypertension, gestatational diabetes mellitus and mode of delivery can affect thyroid hormone status which is inconsistent with our study.

Kim et al., study of perinatal factors affecting cord blood TSH levels performed in 130 neonates in korea revealed that perinatal stress events significantly affect cord blood TSH levels. **Amit gupta et al.,** study revealed that there was no significant difference in cord blood TSH between male and female babies which is consistent with our study. +

Various studies are using different cut-offs for CBTSH levels ranging from 20-90 Miu/ml. We have used the cut-off value for cord blood TSH level as per ROC curve is 13. 1u/ml. **Devi AR and Noushad et al.,**[45] has taken the following range for comparison-CBTSH value <10uu/ml as normal,10-20uu/ml as borderline and >20uu/ml as abnormal. **Gurjit kaur et al.,** from Chandigarh has taken 9uu/ml as the TSH cut off value. Ruth V Mikelsaar et al.,[48] from Estonia has taken CBTSH cut off value of 12uu/ml which is lower cut off value when compared to our study.

In our study 20 cord samples among 110 samples are found to have CBTSH levels above the cut off value of 13. 1 and repeat venous sampling done on 5th day of life. All venous samples TSH levels found to be lower than cut off TSH levels. This reveals that the high cord blood TSH levels are due to perinatal stress factors such as emergency LSCS,resuscitation and low apgar score which has significant positive correlation as evidenced with P values in our study.

LIMITATIONS IN THE STUDY:

To have more conclusive evidence of our findings,

1. We have to evaluate large number of babies

2. To include other maternal and perinatal factors in the analysis.

CONCLUSION OF THE STUDY

As we know that congenital hypothyroidism is the most common preventable cause for mental retardation with an incidence of 1:3000-1:4000[1] live births worldwide and about 1:2500-2800 in India. Therefore neonatal screening for congenital hypothyroidism is very essential using TSH levels either in cord blood or heel prick sample. Cord blood TSH level hence an accepted tool for screening. But it is limited by the fact, that the cord blood TSH have high sensitivity but with high false positive values due to confounding factors. There are various perinatal factors affects cord blood TSH levels. In our study emergency lscs,low apgar score and requirement of resuscitation affects cord blood TSH levels.

RECOMMENDATIONS:

As various perinatal factors influence cord blood TSH levels, knowledge about these factors helps in reliable interpretation of the results and any rise in TSH should be seen in the light of these factors. This helps in avoiding unnecessary repeat evaluation and hence this will saves cost as well as the need to subject for invasive investigations.

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APPENDIX

ANNEXURE-1: PROFORMA

ANNEXURE-2: PATIENT CONSENT FORM

ANNEXURE 3: LIST OF ABBREVIATIONS

PROFORMA

NAME:

AGE:

SEX:

B. WT:

WT APPROPRIATE FOR GESTATION:

APGAR SCORE:

REQUIREMENT FOR RESUSCITATION:

PARITY OF MOTHER:

GESTATIONAL DIABETES MELLITUS:

MODE OF DELIVERY:

LIST OF ABBREVIATIONS USED

TSH	Thyroid Stimulating Hormone
TRH	Thyrotropin Releasing Hormone
MIT	Mono-Iodo Thyronine
DIT	Di-Iodo Thyronine
TRSAb	Thyroid Receptor Stimulating Antibody
TRBAb	Thyroid Receptor Blocking Antibody
TPOAb	Thyroid Antiperoxidase Antibody
TRSI	Thyroid Receptor Stimulating Immunoglobulin
TBG	Thyroid Binding Immunoglobulin

PATIENT CONSENT FORM

Study detail : **"A STUDY ON MEAN TSH LEVELS AND VARIOUS PERINATAL FACTORS AFFECTING TSH LEVEL IN CORD BLOOD OF NEWBORN"**

Study centre :

Patients Name :

Patients Age :

Identification Number :

Patient may check (_/) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. ☐

However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination ☐

Signature/thumb impression: Signature of investigator:

Patients Name and Address: Study investigator's Name:

நோயாளி ஒப்புதல் படிவம்

ஆராய்ச்சியின் விவரம் **"A STUDY ON MEAN TSH LEVELS AND VARIOUS PERINATAL FACTORS AFFECTING TSH LEVEL IN CORD BLOOD OF NEWBORN"**

ஆராய்ச்சி மையம் : அரசு கீழ்பாக்கம் மருத்துவக் கல்லூரி மருத்துவமனை

நோயாளியின் பெயர் : நோயாளியின் வயது:

பதிவு எண் :

நோயாளி கீழ்கண்டவற்றுள் கட்டங்களை (✓) செய்யவும்

1 மேற்குறிப்பிட்டுள்ள ஆராய்ச்சியின் நோக்கத்தையும் பயனையும் முழுவதுமாக புரிந்து கொண்டேன். மேலும் எனது அனைத்து சந்தேங்களையும் கேட்டு அதற்கான விளக்கங்களையும் தெளிவுபடுத்திக் கொண்டேன். ☐

2 மேலும் இந்த ஆராய்ச்சிக்கு எனது சொந்த விருப்பத்தின் பேரில் பங்கேற்கிநேன் என்றும், மேலும் எந்த நேரத்திலும் எவ்வித முன்றிவிப்பு மின்றி இந்த ஆராய்ச்சியிலிருந்து விலக முழுமையான உரிமை உள்ளதையும் இதற்கு எவ்வித சட்ட பிணைப்பும் இல்லை என்பதையும் அறிவேன். ☐

3 ஆராய்சியாளரோ, ஆராய்ச்சி உதவியாளரோ, ஆராய்ச்சி உபயத்தாரரோ, ஆராய்ச்சி பேராசிரியரோ, ஒழுங்குநெறி செயற்குழு உறுப்பினர்களோ எப்போது வேண்டுமானாலும் எனது அனுமதியின்றி எனது உள்நோயாளி மற்றும் புற நோயாளி பதிவுகளை இந்த ஆராய்ச்சிக்காகவோ அல்லது எதிர்கால பிறஆராய்ச்சிகளுக்காகவோ பயன்படுத்திக் கொள்ளலாம் என்றும் மேலும் இந்த நிபந்தனை நான் இவ்வராய்ச்சிலிருந்து தகும் என்றும் ஒப்புக்கொள்கிறேன். ஆயினும் எனது அடையாளம் சம்பந்தப்பட்ட எந்த பதிவகளும் (சட்டபூர்வமான தேவைகள் தவிர) வெளியிடப்படமாட்டது என்ற உறுதிமொழியின் பெயரில் இந்த ஆராய்ச்சிலிருந்து கிடைக்கப்பெறும் முடிவுகளை வெளியிட மறுப்பு தெறிவிக்கமாட்டேன் என்று உறுதியளிக்கிறேன். ☐

4. இந்த ஆராய்ச்சி, அதன் பயன்பாடுகளையும், பின் விளைவுகளையும் அறியும் முயற்சி என்பதை மருத்துவர் மூலம் அறிந்து கொண்டேன். ☐
5. இந்த ஆராய்ச்சிக்கு நான் முழுமனதுடன் சம்மதிக்கின்றேன் என்றும் மேலும் ஆராய்ச்சி குழுவினர் எனக்கு அளிக்கும் அறிவுரைகளை தவறாது பின்பற்றுவேன் என்றும் உறுதியளிக்கிறேன். ☐
6. இந்த ஆராய்ச்சிக்குத் தேவைப்படும் அனைத்து மருத்துவப்பரிசோதனைகளுக்கும் ஒத்துழைப்பு தருவேன் என்று உறுதியளிக்கிறேன். ☐
7. இந்த ஆராய்ச்சிக்கு யாருடைய வற்புறுத்தலுமின்றி எனது சொந்த விருப்பத்தின் பேரிலும் சுயஅறிவுடனும் முழுமனதுடனும் சம்மதிக்கின்றேன் என்று இதன் மூலம் ஒப்புக்கொள்கிறேன். ☐

நோயாளியின் கையொப்பம் / பெருவிரல் கைரேகை

இடம்: தேதி:

ஆராய்ச்சியாளரின் கையொப்பம்:

இடம்: தேதி:

S No	Name	Parity of m	GDM		Gestationa	Weight ap	Mode of d	Birth weig	Sex
1	b/o rajeshv	0	1	0	0	0	0	0	
2	b/o manim	1	0	0	0	0	0	1	
3	b/ovimala	1	0	0	0	0	0	0	
4	b/odhatcha	0	0	1	1	0	1	0	
5	b/osujithra	1	0	0	0	1	0	0	
6	b/o kavitha	1	0	0	0	0	0	1	
7	b/oprema	1	0	0	0	0	1	0	
8	b/opushpa	1	0	0	0	1	0	1	
9	b/o mahala	0	0	1	0	0	0	0	
10	b/okavitha	1	0	0	1	0	0	1	
11	b/orani	1	0	1	0	0	0	0	
12	b/ogayathr	0	0	0	0	0	0	0	
13	b/o raja ka	1	0	0	0	0	0	1	
14	b/otamilma	0	1	0	0	0	0	0	
15	b/okanmar	1	0	1	0	0	1	1	
16	b/o surya	0	0	0	0	1	0	1	
17	b/o amutha	1	0	1	1	0	1	1	
18	b/okeertha	1	0	0	0	0	0	0	
19	b/oshamee	1	0	1	0	0	1	1	
20	b/o kamatc	0	0	0	0	0	0	0	
21	b/osridevi	1	0	0	0	0	0	0	
22	b/opanima	1	1	1	0	1	0	1	
23	b/odeepa	0	0	0	1	0	0	0	
24	b/okannagi	1	0	0	0	0	1	1	
25	b/ojeyaran	1	0	1	1	0	1	1	
26	b/omuniya	1	0	1	0	0	1	0	
27	b/o rajama	1	1	1	0	0	0	0	
28	b/ojeeva	1	0	0	0	0	0	1	
29	b/o samee	0	0	0	0	0	0	0	
30	b/okanimo	0	1	1	0	0	0	1	
31	b/o meena	0	0	0	0	0	0	1	
32	b/o ranjitha	1	0	0	1	0	1	0	
33	b/o banu	0	0	0	0	0	0	0	
34	b/o thanga	0	0	0	0	0	0	0	
35	b/o chellan	1	0	0	1	0	1	1	
36	b/o poovat	0	0	0	0	0	0	1	
37	b/operiyna	1	0	1	0	0	0	0	
38	b/o seetha	0	0	0	0	0	0	0	
39	b/opalania	1	0	0	0	1	0	0	
40	b/o geetha	0	0	0	0	0	0	1	
41	b/o shobar	0	1	1	0	0	1	0	
42	b/o noorul	1	0	0	1	0	0	1	
43	b/o sivakar	1	0	0	0	0	0	1	
44	b/o pooja	0	0	1	0	0	0	0	
45	b/opriya	1	0	0	1	0	1	1	

46	b/oraji	0	0	0	0	0	0	0
47	b/o sangatl	1	0	0	0	0	0	0
48	b/osumath	1	0	1	0	0	0	0
49	b/o chitra	0	0	1	0	0	1	0
50	b/o kanimc	1	0	0	0	0	1	1
51	b/o annapc	1	0	0	0	0	1	0
52	b/oshanthi	0	0	0	1	0	1	1
53	b/ojameela	0	0	0	0	0	0	1
54	b/o ponnur	1	0	0	0	1	0	0
55	b/o balasur	1	0	0	0	0	0	1
56	b/o sindhu	1	1	1	0	0	0	0
57	b/o punitha	1	0	0	0	0	0	0
58	b/oragava	1	0	1	0	0	0	1
59	b/o jeyam	1	0	0	0	0	0	1
60	b/o seetha	0	1	0	0	0	1	1
61	b/okayalviz	0	0	0	0	0	0	0
62	b/opunitha	1	0	0	0	0	0	0
63	b/okala	0	0	0	0	0	0	1
64	b/oparvath	1	0	1	0	0	1	0
65	b/opraveer	1	1	1	0	1	1	0
66	b/o suba	1	0	1	0	1	0	0
67	b/olakshmi	1	0	0	0	0	0	0
68	b/opavithra	1	0	1	0	0	1	0
69	b/o deivana	0	1	0	0	0	0	1
70	b/o kannag	1	0	0	0	0	0	1
71	b/osaritha	0	0	0	1	0	1	1
72	b/o lalitha	0	0	1	0	0	0	1
73	b/o jeniffer	1	1	1	0	0	0	0
74	b/o lakshar	1	0	1	0	0	0	0
75	b/o nisha	1	0	0	0	1	0	1
76	b/opadma	1	0	0	1	0	1	0
77	b/o delphir	0	0	0	0	0	0	0
78	b/o subath	1	0	0	0	0	0	0
79	b/o kayal	1	1	0	0	0	0	0
80	b/osurya	0	0	0	0	0	0	1
81	b/o sangee	0	0	0	0	0	0	0
82	b/o priyank	1	0	0	0	0	0	0
83	b/o kanimc	1	0	0	0	0	0	1
84	b/o rizwana	0	0	0	0	0	0	0
85	b/o sujatha	1	0	1	0	0	0	0
86	b/o nishant	0	0	1	0	0	0	0
87	b/o lakshm	1	1	0	0	1	0	0
88	b/o narmac	0	0	0	0	0	0	1
89	b/o kanimc	1	0	0	0	0	0	1
90	b/o subath	1	0	1	0	1	1	0
91	b/o rani	1	0	0	0	1	0	1
92	b/o stella	1	0	0	1	0	1	0
93	b/o sumith	1	0	1	0	0	0	0
94	b/o kaviya	1	0	1	0	0	0	0
95	b/o kalaira	0	0	0	0	0	0	1

96	b/o sangee	1	0	0	0	0	0	0
97	b/o kundav	1	0	0	0	0	0	0
98	b/o kalpana	1	0	1	0	1	0	1
99	b/o rajeshv	1	0	1	0	0	0	1
100	b/o narmad	1	0	1	0	0	0	0
101	b/o sinnapo	0	1	0	1	0	1	1
102	b/o lingesh	0	0	0	0	0	0	0
103	b/o nandhi	1	0	1	0	0	0	0
104	b/o suguna	0	0	0	0	0	0	0
105	b/o lilly	1	0	0	0	0	0	1
106	b/o karpag	0	0	1	0	0	0	0
107	b/o yasmin	1	1	0	0	0	0	0
108	b/o thenmo	1	0	1	0	0	0	1
109	b/orejina	0	0	0	0	0	0	0
110	b/o kala	1	0	0	0	0	0	0

Apgar	Requireme	TSH value (	venous tsh	ROC cut off >13.1Emergency LSCS	ROC cut off >15.1 Resuscitation	ROC cut off >13.1 APGAR
0	0	10.46		0	0	0
0	0	12.03		0	0	0
0	0	9.97		0	0	0
0	0	11.9		0	0	0
0	1	26.4	11.4	1	1	1
0	0	7.08		0	0	0
0	0	7.59		0	0	0
0	0	21.7	10.5	1	1	1
0	0	7.17		0	0	0
0	0	12		0	0	0
1	1	17.5	11	1	1	1
0	0	8.6		0	0	0
0	0	4.98		0	0	0
1	1	20.7	9.6	1	1	1
0	0	6.4		0	0	0
0	0	23.7	8.8	1	1	1
0	0	12.3		0	0	0
0	0	10.5		0	0	0
0	0	6.8		0	0	0
0	0	5.9		0	0	0
0	0	7.52		0	0	0
0	0	20.6	11.7	1	1	1
0	0	13.1		0	0	0
0	0	4.9		0	0	0
0	0	18.5	11.2	1	1	1
0	0	7.5		0	0	0
0	0	22.1	14.8	1	1	1
0	0	14.2	9	1	0	1
1	1	26.3	12.1	1	1	1
0	0	4.48		0	0	0
0	0	7.81		0	0	0
0	0	12.3		0	0	0
0	0	9.82		0	0	0
0	0	6.54		0	0	0
0	0	22.65	10.9	1	1	1
0	0	11.33		0	0	0
0	0	5.6		0	0	0
0	0	8.4		0	0	0
0	0	15.1	8	1	0	1
0	0	7.3		0	0	0
0	0	7.71		0	0	0
0	0	4.33		0	0	0
0	0	9.1		0	0	0
1	1	24.1	9.8	1	1	1
0	0	13.1		0	0	0

0	0	4.5		0	0	0
0	0	8.39		0	0	0
0	0	7.67		0	0	0
0	0	11.5		0	0	0
0	0	13.1		0	0	0
0	0	15.1	8	1	0	1
0	0	11.6		0	0	0
0	0	5.69		0	0	0
0	0	15.6	8.5	1	1	1
1	1	7.71		0	0	0
0	0	6.843		0	0	0
0	0	6.1		0	0	0
0	0	4.32		0	0	0
0	0	13.1		0	0	0
0	0	11.79		0	0	0
0	0	4.8		0	0	0
1	1	15.2	8	1	1	1
0	0	11.1		0	0	0
0	0	6.5		0	0	0
0	0	9.8		0	0	0
0	0	13.6	8	1	0	1
0	0	8.63		0	0	0
0	0	7.52		0	0	0
0	0	6.62		0	0	0
0	0	4.66		0	0	0
0	0	7.51		0	0	0
0	0	8.32		0	0	0
0	0	4.81		0	0	0
0	0	7.83		0	0	0
0	0	8.81		0	0	0
0	0	4.67		0	0	0
0	0	11.23		0	0	0
0	0	5.42		0	0	0
0	0	9.96		0	0	0
1	0	21.8	12.4	1	1	1
0	0	8.42		0	0	0
0	0	4.65		0	0	0
0	0	7.54		0	0	0
0	0	6.22		0	0	0
0	0	7.13		0	0	0
1	0	7.43		0	0	0
0	0	16.5	9.5	1	1	1
0	0	5.33		0	0	0
0	0	9.34		0	0	0
0	0	23.6	13.33	1	1	1
1	0	13.5	8.5	1	0	1
0	0	6.33		0	0	0
0	0	8.71		0	0	0
0	0	6.33		0	0	0
0	0	7.25		0	0	0

0	0	8.43		0	0	0
0	0	10.13		0	0	0
0	0	24.8	10.9	1	1	1
0	0	4.55		0	0	0
1	1	2.78		0	0	0
0	0	7.46		0	0	0
0	0	6.57		0	0	0
0	0	4.49		0	0	0
0	0	9.52		0	0	0
0	0	5.12		0	0	0
0	0	5.88		0	0	0
0	0	6.57		0	0	0
0	0	5.8		0	0	0
0	0	6.1		0	0	0
0	0	7.08		0	0	0